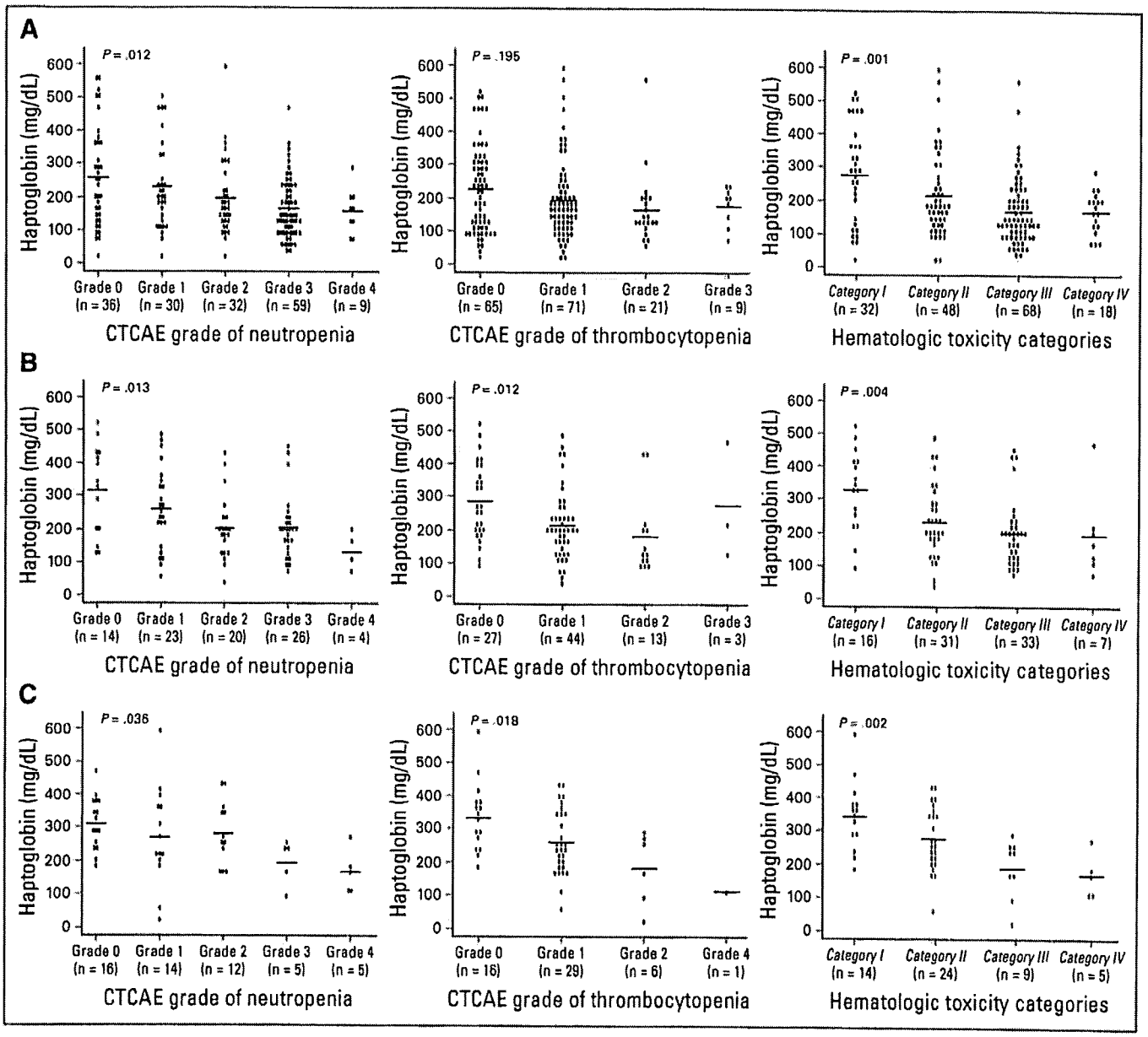

Fig 3. Plasma/serum haptoglobin levels according to the Common Terminology Criteria of Adverse Events (CTCAE; version 3.0). Grades of neutropenia (left), thrombocytopenia (middle), and hematologic toxicity categories (right) in the (A) modeling (M0), (B) validation-1 (V1), and (C) validation-2 (V2) cohorts. Horizontal lines represent the average levels of haptoglobin.

There was no significant difference in age distribution, Eastern Cooperative Oncology Group performance status, liver function, renal function, or prior chemoradiotherapy between the groups (Table 1 and data not shown), indicating that the occurrence of AEs does not merely reflect the general poor condition of patients but is based on certain biologic differences among individuals. We found that individuals who experienced severe AEs after administration of gemcitabine showed decreased baseline levels of plasma haptoglobin (Figs 1B and 2A), and this result was validated in three large cohorts using a different methodology (Fig 3 and Appendix Tables A1 to A3). Haptoglobin is an abundant plasma protein that usually cannot be measured by direct MS. However, constant depletion using an IgY-12 High Capacity Spin Column[32] allowed us to accentuate the differences in haptoglobin levels.

The molecular mechanisms that regulate the plasma haptoglobin level under physiologic and pathologic conditions are largely unknown. Haptoglobin is produced mainly in the liver, taken up by neutrophils, and stored within their cytoplasmic granules. Haptoglobin is released in response to a variety of stimuli, such as infection, trauma, and malignancy,[33] and modulates inflammatory responses. Tumor necrosis factor α induces the release of haptoglobin from neutrophils in vitro.[34] Interestingly, tumor necrosis factor α and its soluble receptors have been reported to be associated with an increased risk of hematologic toxicities.[12,35,36]

Table 2. Contribution of Parameters to Prediction of Hematologic Toxicities Associated With Gemcitabine

Factor	Odds Ratio*	95% CI	P
Haptoglobin level	0.71	0.53 to 0.97	.031†
Phenotype of haptoglobin (v Hp 2-2)			
Hp 2-1	0.61	0.31 to 1.21	.159
Hp 1-1	2.16	0.70 to 6.69	.180
Absolute neutrophil count	0.72	0.61 to 0.86	.0003†
Platelet count	0.63	0.39 to 1.01	.056
Body-surface area	3.86	0.63 to 23.76	.145

NOTE. A forward stepwise selection based on Akaike's Information Criterion was used to select parameters for multivariate analysis.
*Odds ratios are per 100 mg/dL increase for haptoglobin level, per 1,000/μL increase for absolute neutrophil count, per 10×10^4/μL increase for platelet, and per 1.00 m^2 increase for body-surface area.
†$P < .05$.

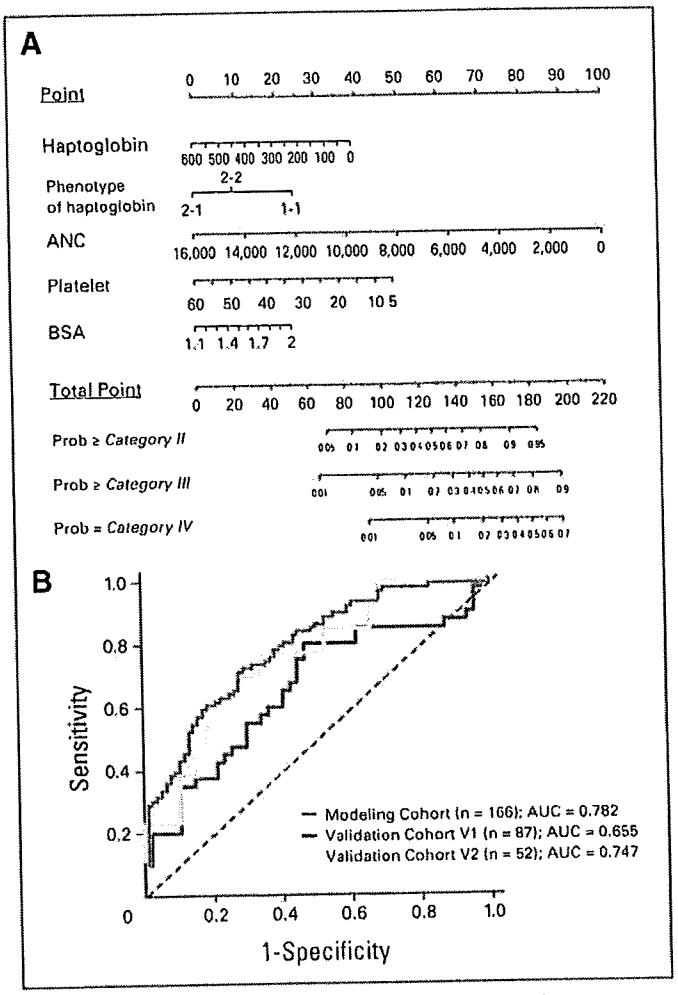

Fig 4. (A) Nomogram to estimate the risk of hematologic toxicities more severe than category II (top), category III (middle), and category IV (bottom). Please see Appendix Figure A4 and its legend for usage. (B) Receiver operating characteristic (ROC) analysis of nomogram for the prediction of category III and IV hematologic toxicities in the modeling (gray), validation-1 (V1; blue), and validation-2 (V2; gold) cohorts. ANC, absolute neutrophil count; BSA, body-surface area; AUC, area under the curve.

To derive clinical applicability from these basic findings, we constructed a model (nomogram) that estimates the possibility of occurrence of hematologic AE before administration of gemcitabine (Fig 4A and Appendix Fig A4). The significance of the model was further confirmed in two independent validation cohorts (Fig 4B). Although its accuracy was far from perfect, the model seems to be practically sufficient for identifying individuals who are likely to suffer from hematologic toxicities after administration of gemcitabine. Various cytotoxic or molecular targeting agents have been tested in combination with gemcitabine in phase III trials, but no apparent additional therapeutic benefit has been demonstrated.[5,6,9,10] The application of this model to patient selection may improve the outcome of such trials. We are now trying to identify new biomarkers that can predict the efficacy of gemcitabine treatment using a similar strategy.

The phenotypes of haptoglobin have been reported to be associated with different hemoglobin-binding, antioxidative, and prostaglandin synthesis–initiating activities.[33] Although haptoglobin phenotype was not significantly associated with hematologic toxicities (Table 1 and Appendix Tables A1 to A3), the average levels of haptoglobin differed among individuals with different phenotypes (Appendix Fig A3), as described previously.[33] For this reason, haptoglobin phenotype was selected in the prediction model by AIC analysis (Table 2). BSA has been repeatedly selected as one of the multivariate parameters for predicting the AEs of anticancer therapies in other studies,[14,37] suggesting a potential lack of accuracy in calculating individually optimized drug dose based solely on BSA, as pointed out previously.[38,39]

In conclusion, we have revealed that a decreased level of haptoglobin is the second most significant factor predicting hematologic toxicities associated with gemcitabine monotherapy after ANC (Table 2). Measurement of haptoglobin is now established as a laboratory test and could be readily incorporated into routine oncologic practice. However, the predictive significance of haptoglobin was revealed only in a retrospective population from a single institution and must, therefore, be validated in an independent prospective multi-institutional study. It was not determined in this study whether haptoglobin could be a predictive biomarker for the AEs of other chemotherapeutic agents. To improve the accuracy of prediction, the discovery of new biomarkers with higher specificity and sensitivity will be necessary. While bearing all these limitations in mind, the present findings may provide novel insights not only into the molecular mechanisms by which gemcitabine causes hematologic toxicities, but also into new avenues for the development of new chemotherapeutic agents with lower toxicity.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Phase III trial of docetaxel plus gemcitabine versus docetaxel in second-line treatment for non-small-cell lung cancer: results of a Japan Clinical Oncology Group trial (JCOG0104)

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Background: This trial evaluated whether a combination of docetaxel and gemcitabine provides better survival than docetaxel alone in patients with previously treated non-small-cell lung cancer (NSCLC).

Patients and methods: Eligibility included pathologically or cytologically proven NSCLC, failure of one platinum-based regimen, performance status of zero or one, 20–75 years old, and adequate organ function. Patients received docetaxel 60 mg/m^2 (day 1) or docetaxel 60 mg/m^2 (day 8) and gemcitabine 800 mg/m^2 (days 1 and 8), both administered every 21 days until disease progression.

Results: Sixty-five patients participated in each arm. This trial was terminated early due to an unexpected high incidence of interstitial lung disease (ILD) and three treatment-related deaths due to ILD in the combination arm. Docetaxel plus gemcitabine compared with docetaxel-alone patients experienced similar grade and incidence of toxicity, except for ILD. No baseline factor was identified for predicting ILD. Median survival times were 10.3 and 10.1 months (one-sided $P = 0.36$) for docetaxel plus gemcitabine and docetaxel arms, respectively.

Conclusion: Docetaxel alone is still the standard second-line treatment for NSCLC. The incidence of ILD is higher for docetaxel combined with gemcitabine than for docetaxel alone in patients with previously treated NSCLC.

Key words: docetaxel, gemcitabine, non-small-cell lung cancer, platinum-refractory, second-line chemotherapy

introduction

Lung cancer is the most common cancer worldwide, with an estimated 1.2 million new cases globally (12.3% of all cancers) and 1.1 million deaths (17.8% of all cancer deaths) in 2000 [1]. The estimated global incidence of non-small-cell lung cancer (NSCLC) in 2000 was ~1 million, which accounted for ~80% of all cases of lung cancer [1]. Treatment of advanced NSCLC is palliative; the aim is to prolong survival without leading to deterioration in quality of life [2]. The recommended first-line treatment of advanced NSCLC currently involves up to four cycles of platinum-based combination chemotherapy, with no single combination recommended over others [3]. Although this treatment improves survival rates, a substantial proportion of patients do progress and should be offered second-line treatment. With unsurpassed efficacy compared with other chemotherapeutic regimens or best supportive care [4, 5], docetaxel alone is the current standard as second-line chemotherapy for advanced NSCLC. The recommended regimen of docetaxel 75 mg/m^2 given i.v. every 3 weeks as second-line therapy has been associated with median survival times of 5.7–7.5 months [4, 5] and is also associated with better quality-of-life outcomes compared with best supportive care [2]. Docetaxel monotherapy for recurrent NSCLC after platinum-based chemotherapy has several limitations, however, including low response rates (7–11%), brief duration of disease control, and minimal survival advantage [4, 5].

Gemcitabine is also active against recurrent NSCLC after platinum-based chemotherapy [6]. Gemcitabine 1000 mg/m^2 once a week for 3 weeks every 28 days produced a 19% response rate in a phase II trial, and it shows significant activity mainly

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in patients previously responsive to chemotherapy [6]. Single-agent gemcitabine has a low toxicity profile and is well tolerated [6].

Docetaxel and gemcitabine have distinct mechanisms of action and nonoverlapping toxic effects except for neutropenia. Many studies of the combination of docetaxel and gemcitabine have been conducted in first- and second-line settings [7–16]. The following doses and schedule have been adopted in most studies: docetaxel 80–100 mg/m^2 on day 1 or 8 and gemcitabine 800–1000 mg/m^2 on days 1 and 8 or on days 1, 8, and 15. Furthermore, most studies required use of prophylactic granulocyte colony-stimulating factor (G-CSF) support.

In Japan, however, the recommended dose of docetaxel is 60 mg/m^2 every 3 weeks [17, 18]. Several studies to confirm the dose and schedule of this combination without prophylactic G-CSF support have been conducted in Japan [19–21]. Two studies recommended docetaxel 60 mg/m^2 on day 8 and gemcitabine 800 mg/m^2 on days 1 and 8, and another study recommended docetaxel 50 mg/m^2 on day 8 and gemcitabine 1000 mg/m^2 on days 1 and 8, without prophylactic G-CSF support, every 3 weeks. These studies demonstrated the consistent promising efficacy of this combination regimen. An objective response was observed in 28%–40% of patients, with a median survival time of 11.1–11.9 months and a 1-year survival rate of 41%–47%.

We conducted a multicenter, randomized, phase III trial to evaluate whether the combination regimen of docetaxel and gemcitabine provides better survival than docetaxel alone in patients with previously treated NSCLC.

patients and methods

patient selection

Eligible patients were 20–75 years of age, with histologically or cytologically confirmed stage IIIB (with malignant pleural effusion or contralateral hilar lymph node metastases) or stage IV NSCLC who had failed one platinum-based chemotherapy regimen previously. Patients who had received gemcitabine or docetaxel were excluded. Additional inclusion criteria included a Eastern Cooperative Oncology Group performance status of zero to one, and adequate organ function as indicated by white blood cell count ≥4000/μl, absolute neutrophil count ≥2000/μl, hemoglobin ≥9.5 g/dl, platelets ≥100 000/μl, aspartate aminotransferase (AST)/alanine amonotransferase (ALT) ≤2.5 times the upper limit of normal, total bilirubin ≤1.5 mg/dl, serum creatinine ≤1.2 mg/dl, and PaO_2 in arterial blood ≥70 torr. Asymptomatic brain metastases were allowed provided that they had been irradiated and were clinically and radiologically stable. Prior thoracic radiotherapy was allowed provided that treatment was completed at least 12 weeks before enrollment. Patients were excluded from the study if they had radiologically and clinically apparent interstitial pneumonitis or pulmonary fibrosis. All patients provided written informed consent, and the study protocol was approved by Japan Clinical Oncology Group (JCOG) Clinical Trial Review Committee and the institutional review board of each participating institution.

treatment plan and dose modifications

Eligible patients were centrally registered at JCOG Data Center and were randomly assigned to either docetaxel 60 mg/m^2 as a 60-min i.v. infusion on day 1 or docetaxel 60 mg/m^2 as a 60-min i.v. infusion on day 8 plus gemcitabine 800 mg/m^2 as a 30-min i.v. infusion on days 1 and 8, using a minimization method with institutions and response to prior chemotherapy (progressive disease or not) as balancing factors. Patients receiving docetaxel were administered standard dexamethasone premedication (8 mg orally at the day before, on the day, and the day after docetaxel administration) as previously reported [7] and 50 mg of diphenhidramine 30 min before docetaxel administration. Recombinant human G-CSF was not given prophylactically. Chemotherapy cycles were repeated every 3 weeks until disease progression. Docetaxel was given before gemcitabine in the docetaxel plus gemcitabine regimen.

Dose adjustments were based mainly on hematologic parameters. The doses of docetaxel and gemcitabine were reduced by 10 and 200 mg/m^2, respectively, in subsequent cycles if chemotherapy-induced febrile neutropenia, grade 4 anemia, grade 4 thrombocytopenia, grade 4 leukopenia, or grade 4 neutropenia lasting for >3 days occurred in the absence of fever. Dose reductions were maintained for all subsequent cycles. Patients requiring more than one dose reduction were off-protocol treatment.

baseline and follow-up assessments

Pretreatment evaluation included a complete medical history and physical examination, a complete blood count (CBC) test with differential and platelet count, standard biochemical profile, electrocardiogram, chest radiographs, computed tomographic scans of the chest, abdomen, and brain, magnetic resonance imaging, and a whole-body bone scan. During treatment, a CBC and biochemical tests were carried out weekly. A detailed medical history was taken and a complete physical examination with clinical assessment was carried out weekly to assess disease symptoms and treatment toxicity, and chest radiographs were done every treatment cycle. Toxicity was evaluated according to the National Cancer Institute Cancer—Common Toxicity Criteria Version 2 [22].

All patients were assessed for response by computed tomography scans after every two cycles of chemotherapy. Response Evaluation Criteria in Solid Tumors (RECIST) were used for the evaluation of response [23].

The progression-free survival (PFS) was calculated from the day of randomization until the day of the first evidence of disease progression or death. If the patient had no progression, PFS was censored at the day when no clinical progression was confirmed. Overall survival (OS) was measured from the day of randomization to death.

Disease-related symptoms were evaluated and scored at baseline and 6 weeks after the start of treatment with the seven-item Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung version 4 [24], which were translated from English to Japanese. The questionnaire entries were listed as follows: 'I have been short of breath', 'I am losing weight', 'My thinking is clear', 'I have been coughing', 'I have a good appetite', 'I feel tightness in my chest', and 'Breathing is easy for me'. Patients scored using a five-point Likert scale (0–4) by themselves. The maximum attainable score of the LCS was 28, where the patient was considered to be asymptomatic.

statistical analysis

The primary endpoint was OS; secondary endpoints were PFS, the overall response rate, disease-related symptoms, and toxicity profile. Based on previous trials evaluating the docetaxel [4, 5] and docetaxel plus gemcitabine [19–21] regimens, the present study was designed to detect a 12% difference of 1-year survival rate. To attain an 80% power at a one-sided significance level of 0.05, assuming 1-year survival of docetaxel arm as 35% with 1 year of follow-up after 2 years of accrual, 284 patients (142 per each arm) were required. Analyses were to be carried out with all randomized patients. Both the OS and PFS were estimated with the Kaplan–Meier method. The comparisons of OS and PFS between arms were assessed by the stratified log-rank test with a factor used at randomization, response to prior chemotherapy. Two interim analyses were planned after half of the patients were registered and the end of registration.

For the symptom analysis, changes of LCS from initial score were compared between arms using analysis of covariance with initial score as a covariate.

All analyses were carried out with SAS software release 8.2 (SAS Institute, Cary, NC).

results

This trial was terminated early due to the unexpected high incidence of interstitial lung disease (ILD) and three treatment-related deaths due to ILD in the combination arm, which were identified by the Adverse Event Reporting system.

patient characteristics

From January 2002 to September 2003, 130 patients with NSCLC who had failed prior platinum-based chemotherapy from 32 institutions were enrolled (Appendix). These patients were randomly assigned to docetaxel alone ($n = 65$) or docetaxel plus gemcitabine ($n = 65$). One patient died as a result of rapid progressive disease before chemotherapy administration, and one patient did not meet the entry criteria in the docetaxel arm. In addition, one patient did not meet the entry criteria in the docetaxel plus gemcitabine arm. All patients were included in the analysis of survival and PFS, and 64 docetaxel and 65 docetaxel plus gemcitabine patients were assessable for toxicity. Fifty-nine patients with measurable lesions by RECIST in the docetaxel arm and 57 eligible patients in docetaxel plus gemcitabine arm were assessable for response (Figure 1). Table 1 presents baseline patient characteristics.

The median number of cycles was 3 (range 0–6) and 2 (range 1–8) in the docetaxel and docetaxel plus gemcitabine arms, respectively. The median interval between cycles was 22 days for both arms.

toxicity

This trial was terminated early due to the unexpected high incidence of ILD and three treatment-related deaths (4.6%) due to ILD in the docetaxel plus gemcitabine arm. These events were identified by the Adverse Event Reporting system. Thirteen (20.0%) patients receiving combination treatment suffered from all grades of ILD, whereas only two (3.1%) patients receiving docetaxel alone suffered from grades 1–2 ILD. Grades 2–4 ILD occurred in 16.9% of docetaxel plus gemcitabine patients, an unexpected high incidence rate. No risk factors were identified contributing to these pulmonary adverse events.

Toxicity was assessed in all patients who received at least one treatment cycle and in all cycles (Table 2). Overall, grades 3–4 neutropenia occurred in 55 docetaxel patients (85.9%) and 53 docetaxel plus gemcitabine patients (81.5%). Grades 3–4 anemia occurred in two patients (3.1%) and 12 patients (18.5%) treated with docetaxel alone and docetaxel plus

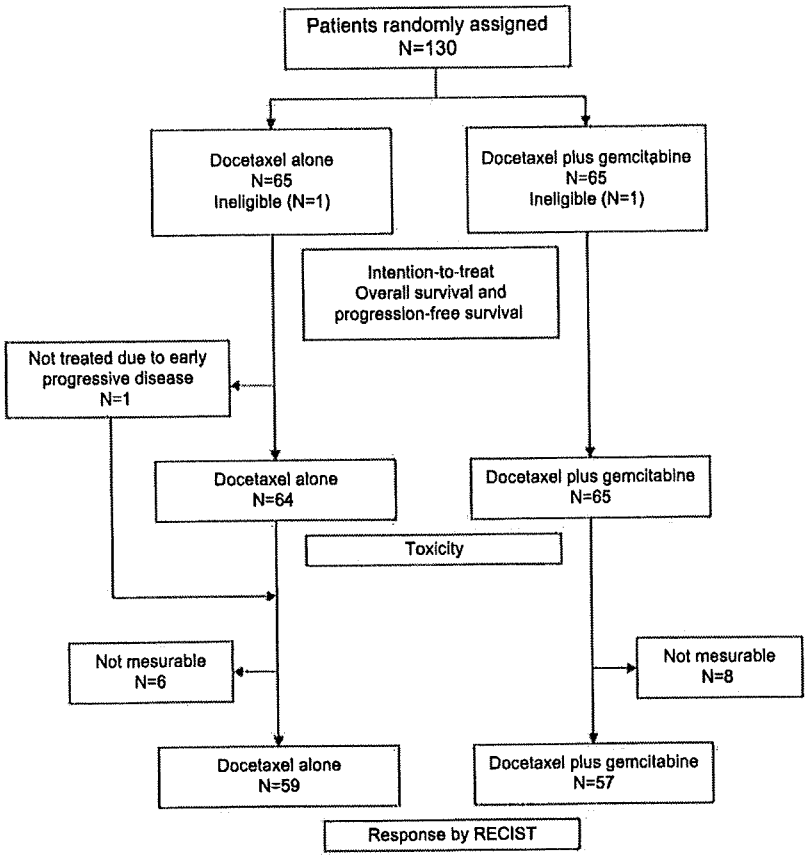

Figure 1. CONSORT diagram for the study.

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gemcitabine, respectively. Sixteen patients treated with docetaxel (25.0%) and 11 patients with docetaxel plus gemcitabine (16.9%) developed febrile neutropenia. All required antibiotic treatment and G-CSF; however, no patient died. One patient in the docetaxel plus gemcitabine arm developed anaphylatic shock immediately after administration of docetaxel at the second cycle. Grades 2–4 ALT elevation was more frequent with docetaxel plus gemcitabine than with docetaxel (20.0% versus 4.7%). Grades 2–4 non-neutropenic infection occurred more often with docetaxel plus gemcitabine than with docetaxel (21.5% versus 15.6%). Grades 2–4 ILD was more frequent with docetaxel plus gemcitabine than with docetaxel (16.9% versus 1.6%). Other toxic effects were relatively mild (Table 2). Overall, docetaxel plus gemcitabine was more toxic than docetaxel, however, well tolerated except for ILD in docetaxel plus gemcitabine arm.

Table 1. Patient characteristics

	D arm		DG arm	
	No. of patients	%	No. of patients	%
Patients enrolled	65		65	
Age, years				
Median	62		60	
Range	34–75		34–74	
Gender				
Male	48	73.8	51	78.5
Female	17	26.2	14	21.5
ECOG PS				
0	20	30.8	21	32.3
1	45	69.2	44	67.7
Histology				
Squamous	19	29.2	22	33.8
Adenocarcinoma	40	61.5	40	61.5
Large cell	4	6.2	3	4.6
Others	2	3.1	0	0
Best response of prior chemotherapy				
CR	2	3.1	0	0
PR	38	58.5	40	61.5
SD	20	30.8	19	29.2
PD	5	7.7	6	9.2

D, docetaxel; DG, docetaxel plus gemcitabine; ECOG PS, Eastern Cooperative Oncology Group performance status; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

treatment efficacy

The overall response rate for docetaxel alone was 6.8% [95% confidence interval (CI) 1.9% to 16.5%] and 7.0% for docetaxel plus gemcitabine (95% CI 2.0% to 17.0%). There was no significant difference between treatment arms ($P = 0.71$; Fisher's exact test).

At the time of this analysis, 50 docetaxel patients (76.9%) and 48 docetaxel plus gemcitabine patients (73.8%) had died. The median survival time was 10.1 months for docetaxel alone and 10.3 months for docetaxel plus gemcitabine (one-sided $P = 0.36$ stratified log-rank test; Figure 2A). The respective 1-year survival rate was 43.1% (95% CI 31.0% to 55.1%) for docetaxel and 46.0% (95% CI 33.8% to 58.1%) for docetaxel plus gemcitabine.

The median PFS time was 2.1 and 2.8 months for docetaxel and docetaxel plus gemcitabine, respectively (one-sided $P = 0.028$ stratified log-rank test; Figure 2B).

Table 2. Hematological and non-hematological toxicity

	D arm (n = 64) NCI-CTC grade					DG arm (n = 65) NCI-CTC grade				
Hematological	0–1	2	3	4	3–4%	0–1	2	3	4	3–4%
Anemia	27	35	2	0	3.1	21	32	9	3	18.5
Leukopenia	9	14	29	12	64.1	11	12	32	10	64.6
Neutropenia	7	2	15	40	85.9	8	4	19	34	81.5
Thrombocytopenia	64	0	0	0	0	43	14	8	0	12.3
Non-hematological	0–1	2	3	4	2–4%	0–1	2	3	4	2–4%
Allergic reaction	64	0	0	0	0	59	5	1	0	9.2
Alopecia	45	18	–	–	28.1	49	14	–	–	21.5
ALT	61	2	1	0	4.7	52	10	3	0	20.0
Diarrhea	61	3	0	0	4.7	60	3	2	0	7.7
Edema	63	1	0	0	1.6	64	1	0	0	1.5
Fatigue	56	5	2	1	12.5	56	7	1	1	13.8
Febrile neutropenia	48	–	16	0	25.0	54	–	11	0	16.9
Infection with grades 3–4 neutropenia	59	–	5	0	7.8	56	–	9	0	13.8
Infection without neutropenia	54	8	2	0	15.6	51	4	9	1	21.5
Nausea	55	7	2	–	14.1	55	6	4	–	15.4
Neuropathy	62	2	0	0	3.1	62	2	0	1	4.6
Pneumonitis (ILD)	63	1	0	0	1.6	54	3	7	1	16.9
Stomatitis	61	3	0	0	4.7	60	5	0	0	7.7

D, docetaxel; DG, docetaxel plus gemcitabine; NCI-CTC, National Cancer Institute—Cancer Common Toxicity Criteria; ALT, alanine aminotransferase; ILD, interstitial lung disease.

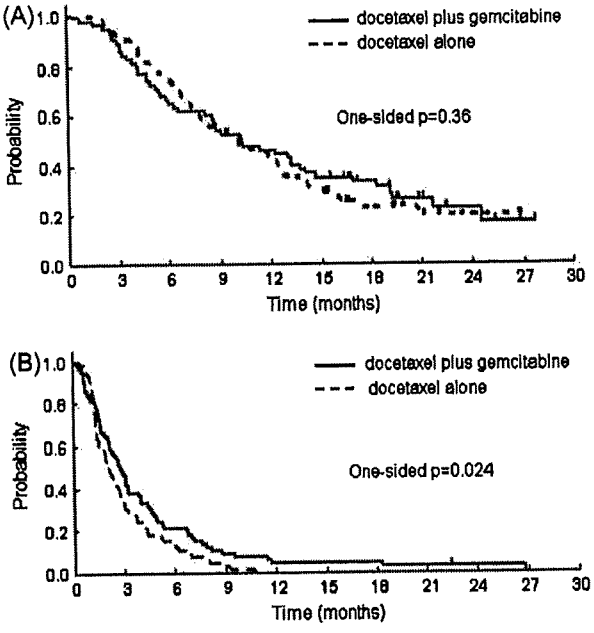

Figure 2. Overall survival (A) and progression-free survival (B) by treatment arm.

disease-related symptom assessment

Patients' compliance with disease-related symptom assessment was 100% at baseline and 95.4% at 6 weeks later. Compliance rates were not different between the arms ($P = 1.00$). LCS data were missing in four surveys due to death or severe impairment of the patient's general condition; this accounted for 1.5% of the total number of surveys scheduled. Mean LCS at baseline and 6 weeks were shown in Table 3. There were no significant differences in the LCS changes from baseline to 6 weeks between docetaxel and docetaxel plus gemcitabine arms ($P = 0.61$).

discussion

This trial was terminated early due to the unexpected high incidence of ILD and three treatment-related deaths due to ILD in the docetaxel plus gemcitabine arm. Our findings seem to indicate that the combination of docetaxel and gemcitabine may be associated with a higher incidence of pulmonary adverse events compared with docetaxel alone, especially in patients with previously treated NSCLC.

Pulmonary toxicity following chemotherapeutic agents, including ILD, has been well recognized for many years. In most cases, this toxicity is mild and self-limiting. However, the mechanism of developing drug-induced ILD is uncertain, and risk factors for developing this disorder have not been identified. In terms of combination therapy with docetaxel and gemcitabine for advanced NSCLC, there were few reports about the incidences of ILD at the time this study was planned. A phase I study of patients with transitional cell carcinoma evaluated thrice-weekly doses of docetaxel given on day 1 plus gemcitabine given on days 1 and 15 and showed that pulmonary toxicity occurred in three of five patients and was

Table 3. Disease-related symptom assessment

Lung Cancer Subscale	D arm	DG arm
Baseline		
Number	$n = 65$	$n = 65$
Mean ± SD	19.0 ± 5.48	19.7 ± 5.25
6 weeks later		
Number	$n = 62$	$n = 62$
Mean ± SD	18.1 ± 5.56	18.9 ± 5.05
Difference		
Mean ± SD	−1.11 ± 3.81	−0.99 ± 4.49

D, docetaxel; DG, docetaxel plus gemcitabine; SD, standard deviation.

the cause of death in one [25]. Recently, some reports have been published about the high incidence of ILD due to the combination regimen of docetaxel and gemcitabine in patients with NSCLC [13, 26, 27], including the present study (Table 4). In Japanese population, ILD is a very complex issue in treatment of patients with lung cancer. Epidermal growth factor tyrosine kinase inhibitor gefitinib is developing ILD significantly in Japanese patients with NSCLC [28]. It is uncertain why ILD is developing more in Japanese patients with NSCLC than the Western patients. Ethnic difference may be one of the explanations for this occurrence. The combination of gemcitabine and docetaxel is associated with a high incidence of severe pulmonary toxicity. The regimen should not be used outside a clinical trial.

The median survival times of 10.1 and 10.3 months and estimated 1-year survival rates of 43.1% and 46.0% with docetaxel alone and docetaxel plus gemcitabine, respectively, suggest that adding gemcitabine to docetaxel did not provide any increased efficacy in patients with previously treated NSCLC. Interestingly, the combination regimen of docetaxel plus gemcitabine significantly improved the median PFS time ($P = 0.028$). Possible reasons for failing to detect a significant difference between survival curves may include an insufficient occurrence of documented events as a result of the study population comprising patients with relatively good prognosis, in addition to a high proportion of patients subsequently receiving third-line therapy. During this study, gefitinib treatment was commonly used for patients with recurrent NSCLC in Japan [29]. Asian ethnicity is a well-known predictive factor for a response for gefitinib [30].

Two randomized phase II trials compared docetaxel alone with docetaxel plus irinotecan in second-line chemotherapy for NSCLC [31, 32]. No significant treatment differences in survival were observed in either trial; however, the trials were phase II study and were not powered or designed to compare survival. This study was not powered to compare survival when it was terminated early due to the unexpected high incidence of ILD in the docetaxel plus gemcitabine arm. However, based on previous studies, as well as the present results, combination chemotherapy with docetaxel and another chemotherapeutic agent has not improved survival in patients with previously treated NSCLC.

In conclusion, docetaxel alone is still the standard second-line treatment for advanced NSCLC. The combination of docetaxel and gemcitabine was too toxic to obtain any survival

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Table 4. Reports of interstitial lung disease due to docetaxel plus gemcitabine regimen

Author	Year	Study type	Treatment schedule	*n*	Grades 3–4 ILD (%)	TRD (%)
Rebattu et al. [13]	2001	Phase I/II	Docetaxel (60, 75, 85, 100 mg/m^2) day 8; gemcitabine (1000 mg/m^2), days 1 and 8, every 3 weeks	49	3 (6.1)	0
Kouroussis et al. [25]	2004	Phase I	Docetaxel (30, 35, 40 mg/m^2), days 1, 8 and 15; gemcitabine (700, 800, 900, 1000 mg/m^2), days 1, 8 and 15, every 4 weeks	26	6 (23)	2 (7.7)
Matsui et al. [21]	2005	Phase I/II	Docetaxel (50, 60 mg/m^2) day 1 or 8; gemcitabine (800, 1000 mg/m^2), days 1 and 8, every 3 weeks	59	3 (5.1)	0
Pujor et al. [27]	2005	Phase III	Docetaxel (85 mg/m^2) day 8; gemcitabine (1000 mg/m^2), days 1 and 8, every 3 weeks	155	8 (5.2)	1 (0.6)
			Cisplatin (100 mg/m^2) day 1; vinorelbine (30 mg/m^2), days 1, 8, 15 and 22, every 4 weeks	156	1 (0.6)	0
Takeda (present study)	2008	Phase III	Docetaxel (60 mg/m^2) day 8; gemcitabine (800 mg/m^2), days 1 and 8, every 3 weeks	65	8 (12.3)	3 (4.6)
			Docetaxel (60 mg/m^2) day 1, every 3 weeks	64	0 (0)	0

ILD, interstitial lung disease; TRD, treatment-related death.

benefit in patients with recurrent advanced NSCLC. The development of less toxic and more effective chemotherapeutic agents, including molecular targeted drugs, is warranted for the second-line treatment of NSCLC.

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appendix

The following institutions participated in the study: Hokkaido Cancer Center (Sapporo), Ibaragi Prefectural Central Hospital (Kasama), Tochigi Cancer Center (Utsunomiya), Nishigunma National Hospital (Shibukawa), Gunma Prefectural Cancer Center Hospital (Ohta), Saitama Cancer Center Hospital (Ina), National Cancer Center Hospital East (Kashiwa), National Cancer Center Hospital (Tokyo), International Medical Center of Japan (Tokyo), Cancer Institute Hospital (Tokyo), Toranomon Hospital (Tokyo), Kanagawa Cancer Center Hospital (Yokohama), Yokohama Municipal Hospital (Yokohama), Niigata Cancer Center Niigata Hospital (Niigata), Gifu Municipal Hospital (Gifu), Aichi Cancer Center Hospital (Nagoya), Nagoya National Hospital (Nagoya), Prefectural Aichi Hospital (Okazaki), Osaka City University Medical School (Osaka), Kinki University School of Medicine (Osaka-Sayama), Osaka Medical Center for Cancer and Cardiovascular Disease (Osaka), Osaka Prefectural Medical Center for Respiratory and Allergic disease (Habikino), Kinki-Chuo Chest Medical Center (Sakai), Toneyama National Hospital (Toyonaka), Osaka Prefectural General Hospital (Osaka), Osaka City General Hospital (Osaka), Kobe City General Hospital (Kobe), Hyogo Collage of Medicine (Nishinomiya), Hyogo Cancer Center (Akashi), Shikoku Cancer Center Hospital (Matsuyama), Kyusyu University Hospital (Fukuoka), and Kumamoto Regional Medical Center (Kumamoto).

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Reasons for response differences seen in the V15-32, INTEREST and IPASS trials

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Abstract | The first phase III study to assess the effect of gefitinib and docetaxel on the survival of Japanese patients with non-small-cell lung cancer who received previous treatment with platinum doublets, the V15-32 trial, did not establish noninferiority of gefitinib over docetaxel in terms of the effect on overall survival, despite the results showing a twofold higher response rate to gefitinib. The overall survival favored docetaxel for the first 18 months and gefitinib thereafter. The INTEREST trial, which compared docetaxel and gefitinib, demonstrated noninferiority of gefitinib, and the survival curves were completely superimposed. In this trial, patients had been recruited from 24 countries from Europe, Asia, and North and South America. Results of the IPASS trial showed superior progression-free survival for gefitinib compared with the combination of carboplatin and paclitaxel as first-line treatment in Asian patients who were nonsmokers and had adenocarcinoma histology. In this Review, we discuss the reasons for the differences in the effects of molecular-targeted drugs and cytotoxic antineoplastic agents observed in these trials. We also highlight the magnitude of the antitumor activity of these two different categories of drugs, and discuss how this could affect future clinical trial design and analysis.

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Introduction

At present, the consensus opinion is that the efficacy of lung cancer chemotherapy with cytotoxic agents has reached a plateau, and it is difficult to expect superior efficacy with any novel cytotoxic anticancer agents that will become available in the near future. It is generally believed that the results seen with different platinum doublet regimens are of a similar magnitude, no matter which combination is used. However, slight differences were seen in results reported by the Eastern Cooperative Oncology Group (ECOG) study,[1] Four Arm Clinical Study (FACS),[2] South Western Oncology Group (SWOG) trial,[3] and Tax 326 study.[4] In the ECOG trial, progression-free survival seen with gemcitabine plus cisplatin was better than in the other treatment arms that included paclitaxel plus cisplatin, docetaxel plus cisplatin and paclitaxel plus carboplatin.[1] In the FACS trial, the overall survival rates observed for carboplatin plus paclitaxel and cisplatin plus vinorelbine were inferior compared with the gemcitabine plus cisplatin and irinotecan plus cisplatin,[2] and overall survival of cisplatin plus docetaxel was significantly better than that of cisplatin and vinorelbine.[4] In everyday clinical practice, treatment arms are selected taking into consideration factors such as the toxicity profile and ease of use on an outpatient basis. The choices of treatment used in combination with radiation therapy and surgery are based on consideration of patient adherence to the drugs administered.

Clinical outcomes with EGFR inhibitors

EGFR is a member of the HER family, which consists of four members: EGFR/HER1/erbB1, HER2/neu/erbB2, HER3/erbB3, and HER4/erbB4.[5] Once the ligands bind to the extracellular domain of EGFR proteins, the receptors dimerize with other EGFR family members to form homodimers or heterodimers, which induce phosphorylation of the tyrosine kinase EGFR and activation of downstream signal pathways.[6] EFGR-tyrosine kinase inhibitors (EGFR-TKIs) are molecular-targeted drugs that, in general, target the ATP binding site of protein kinases and show competitive inhibition, thereby preventing correct functioning of the receptor in tumor cells. Great advances are expected in the treatment of non-small-cell lung cancer (NSCLC) when these agents become available because they have demonstrated impressive tumor shrinkage in patients with disease refractory to platinum and taxane therapy even in phase I clinical trials.[7–9] It has been difficult to demonstrate any survival benefit of these agents in the clinical setting.[10–13] In phase III studies that compared erlotinib with placebo as second-line and third-line chemotherapy, a survival benefit in favor of erlotinib was demonstrated. In the ISEL (Iressa Survival Evaluation in Lung Cancer) trial that compared gefitinib with placebo in similar populations of patients, no survival advantage was seen with gefitinib; however, significant prolongation of survival

Competing interests
N. Saijo has declared associations with the following companies: AstraZeneca, Bristol-Myers Squibb, Chugai-Roche, and Eli Lilly. H. Kunitoh declared associations with the following companies: AstraZeneca, Bristol-Myers Squibb and Sanofi-Aventis. See the article online for full details of the relationships. M. Takeuchi declared no competing interests.

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Key points

- Many unexpected results were observed in the randomized, controlled trials of EGFR-targeted tyrosine kinase inhibitors (TKIs)
- The nature and quantity of antitumor effects are different between cytotoxic chemotherapy and molecular-targeted drugs
- Selection of patients is extremely important for future clinical trials that test EGFR-TKIs
- Results from the IPASS trial demonstrate that EGFR-TKIs provide superior progression-free survival compared with platinum-based doublet chemotherapy in selected patients with non-small-cell lung cancer, especially those with mutated *EGFR*

Table 1 | Data from randomized, controlled trials of EGFR-TKIs for NSCLC treatment

Study	EGFR-TKI agent	Selection of patients	Difference in end points between treatment and control
ISEL[3]	Gefitinib vs placebo	None	Negative
BR.21[5]	Erlotinib vs placebo	None	Positive
INTACT 1&2	Gefitinib vs combination	None	Both negative
TALENT & TRIBUTE[6]	Erlotinib vs combination	None	Both negative
V15-32	Gefitinib vs docetaxel	Japanese	Negative
INTEREST[7]	Gefitinib vs docetaxel	None	Positive
IPASS	Gefitinib vs carboplatin plus PTL	Adenocarcinoma, Asian, nonsmoking	Positive
WJTOG0203	Gefitinib vs platinum doublet (consolidation)	Japanese	Not available

[a]Discrepancies: BR.21 versus TALENT & TRIBUTE; ISEL versus INTEREST. Abbreviations: NSCLC, non-small cell lung cancer; PTL, paclitaxel, irastuzumab and Japan not TKI; tyrosine kinase inhibitor.

time was observed in Asian patients.[4,13] Four large, randomized, controlled trials of standard platinum-based chemotherapy (carboplatin plus paclitaxel or cisplatin plus gemcitabine) with or without EGFR-TKIs yielded negative results in patients with advanced NSCLC who had not received previous chemotherapy.[3,5,6] In addition, the SWOG trial showed that the intensification with gefitinib after chemoradiotherapy in stage III NSCLC provided significantly poorer survival than in the control group.[14] As the reported response rates to EGFR-TKIs in Western populations are ≤10%, this low percentage does not reflect the prolongation of survival.

By contrast, gefitinib has been found to have outstanding therapeutic effect in a phase II clinical trial of Japanese patients, with reported response rates of 27.5%, median duration of response of 114 days, and median survival time of 13.8 months.[16] Subsequent clinical trials that included Asian populations showed higher response rates and better survival rates associated with this drug compared with placebo;[14,17] however, no such benefit was seen in Western patients.[14] A phase II trial of gefitinib in nontreated, nonselected, Japanese patients with NSCLC produced a similar response rate compared to patients with previous therapy.[18] Analysis of clinical factors has demonstrated that Asian ethnicity, female gender, adenocarcinoma histology and nonsmoking status are favorable factors in relation to the efficacy of EGFR-TKIs.[19–22]

In 2004, the presence of activating mutations of *EGFR* in tumor cells was reported to be extremely important for achieving the antitumor effect of EGFR-TKIs.[23,24] In patients with these *EGFR* mutations the response rate to EGFR-TKIs is approximately 80%.[23–25] The response duration ranged from 7.0 months to 10.7 months. The frequency of *EGFR* mutations is higher in Asian populations (30–40%) compared with Western populations (5–10%).[23] A higher frequency of these mutations in Japanese populations was also shown to correlate with the presence of favorable clinical factors such as adenocarcinoma, female gender and nonsmoking status.[26–28] Some have suggested that other biomarkers, such as *EGFR* amplification status detected by fluorescent *in situ* hybridization, could also be useful indicators of the response to EGFR-TKIs; however, these biomarkers are not reliable.[29,30] The problem with results obtained using fluorescent *in situ* hybridization is that this technique might detect two genetic abnormalities, namely, *EGFR* amplification and high polysomy. High polysomy is usually not well-correlated with the presence of *EGFR* mutations.[31–33] In Japan, gefitinib has been approved by the Ministry of Health, Welfare and Labour on the basis of data from the IDEAL (phase II) study and data from trials showing the survival benefit of gefitinib in Japanese populations.

Data from the V15-32 study of gefitinib

Two randomized, controlled trials conducted in Western patients have reported the effects of docetaxel in patients with previously treated NSCLC.[34,35] Prolongation of survival was demonstrated in the docetaxel-treated groups compared with groups given best supportive care or treated with ifosfamide and/or vinorelbine. Docetaxel was, therefore, established as the gold standard for second-line chemotherapy in patients with NSCLC.[35,36] No data, however, compared the activities of docetaxel and placebo in the second-line setting in Japan. On the basis of comparative studies of pemetrexed and docetaxel, pemetrexed is now employed more frequently in the US for treating patients with NSCLC in the second-line setting.[37] In Japan, however, pemetrexed has not been approved for use in patients with lung cancer because insufficient studies in Japanese populations have been carried out, even though a clinical phase II study has been completed.[38] There has also been a report describing the superiority of erlotinib in prolonging the survival of previously treated patients with NSCLC compared with best supportive care in the second-line or third-line setting.[39] This drug has just been approved for treatment of lung cancer in Japan.[40]

V15-32 was an open-label, randomized phase III study that compared 250 mg gefitinib with 60 mg/m^2 docetaxel in Japanese patients with NSCLC and a history of failure of one or two chemotherapy regimens (Figure 1).[41] The main purpose of this study was to demonstrate the

noninferiority of gefitinib over docetaxel for overall survival in these patients, according to predefined criteria (that is, upper threshold of the CI of the hazard ratio [HR] less than 1.25). A total of 484 patients were accrued, with 242 in each treatment arm; however, noninferiority of gefitinib for overall survival could not be established (HR 1.12; 95% CI 0.89–1.40), and no significant difference in overall survival was apparent between the two treatment groups ($P = 0.330$). A Cox regression analysis, with adjustments for imbalances in the baseline characteristics of the patients, yielded an HR of 1.01 (95% CI of 0.80–1.27), $P = 0.914$ (Table 2 and Figure 2).[1] Secondary end points included progression-free survival, time-to-treatment failure, response rate, and disease control rate. These end points were evaluated in the patients who had measurable target lesions at study entry. Gefitinib treatment was associated with a significantly improved overall response rate (22.5% versus 12.8%, $P = 0.009$) and time-to-treatment failure (HR 0.63; 95% CI 0.51–0.77, $P < 0.001$). No significant differences in progression-free survival (HR 0.90; 95% CI 0.72–1.12, $P = 0.335$) or disease control rate (34% versus 33.2%, $P = 0.735$) were seen between the two treatment groups.[1] Since cessation of chemotherapy in those without disease progression was included as an event for time-to-treatment failure, comparison of this end point between docetaxel and gefitinib-treated patients would not have much clinical relevance.

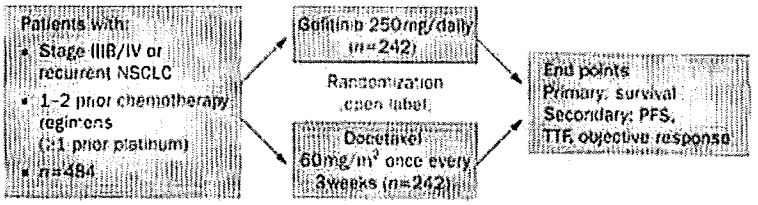


Figure 1 | Schematic diagram to show the randomization schema for the randomized phase III V15-32 trial. Abbreviations: NSCLC, non-small-cell lung cancer; PFS, progression-free survival; TTF, time-to-treatment failure. Data courtesy of AstraZeneca.

Additional analysis of V15-32

On behalf of the Drug Safety Policy Panel and FDA Safety Investigation Committee, Takeuchi stated the following on the basis of results of the V15-32 trial.[2] Firstly, the two groups were well balanced and met the requirements of randomization, which assured the comparability of the groups. Secondly, the hazard ratios in two comparative groups on Cox regression analysis should remain constant regardless of the passage of time. In the current study, it does not seem likely that this prerequisite was met; it is difficult, therefore, to evaluate the therapeutic results from the major outcome of the analysis, because the HRs were assumed to be constant regardless of the passage of time.

To understand how the therapeutic benefit in the gefitinib group, compared with the docetaxel group, changed in a time-dependent manner, Takeuchi conducted a retrospective, exploratory investigation of the effect at various time intervals, using survival rate as the evaluation index. In terms of the survival rate at an early stage of follow-up (that is, less than 1 year) the CI for the therapeutic effect indicated that docetaxel was superior to gefitinib. After about 24 months, however, the results showed a tendency for gefitinib to be superior to docetaxel. The CI was so wide that it was difficult to conclude that gefitinib was indeed superior to docetaxel at this stage (Figure 3).

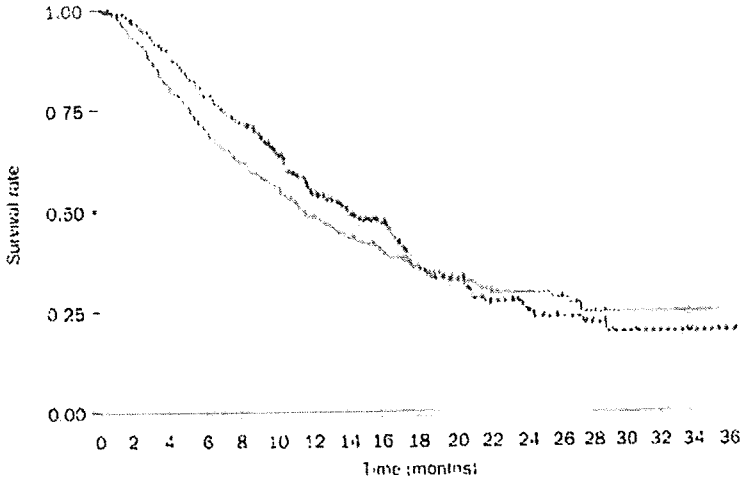
Interpretation of the results of V15-32

The V15-32 study was the first comparative, large-scale, randomized trial conducted in previously treated patients with NSCLC in Japan. It is highly noteworthy that 490 patients were recruited within a period of about 2.5 years and accurate results were obtained. The median survival rates for docetaxel and gefitinib were 11.5 and 14.0 months, respectively. Despite the problems related to selection of patients, the results showed the high level of medical care in Japan. The initial hypothesis of noninferiority of gefitinib was not established. This finding implies that there might be a high probability of gefitinib being inferior to docetaxel for treating patients with NSCLC in the second-line setting. Docetaxel, therefore, remains the drug of first choice in these patients. As subset analyses could not identify subgroups of patients in whom gefitinib yielded better outcomes than docetaxel, a 'docetaxel-first' policy should be employed even in patients with a favorable risk profile (that is, females, adenocarcinoma histology and never-smokers). The response rates of patients to gefitinib were greater than 20%, and almost double that seen with docetaxel. Although the study was small, some of the patients treated with gefitinib have shown prolonged progression-free survival, and the survival curve of the gefitinib group crossed over the survival curve for the docetaxel group 18 months after treatment initiation.[3] These results strongly suggest that gefitinib could be beneficial in a subset of docetaxel-resistant and docetaxel-intolerant patients. The results of the primary analysis of gefitinib versus docetaxel have neither confirmed nor refuted these effects of gefitinib.[4] For the first 18 months after initiation of treatment, the survival rate was better in the docetaxel group than in the gefitinib group; the reasons for this finding may be hypothesized as follows: first, gefitinib might promote tumor proliferation; second, gefitinib might exert potent toxicity in some patients; and third, the antitumor activity of docetaxel might be superior in the overall population of patients. It is likely that the third reason could explain the better survival rate of the docetaxel group, and the late benefit of gefitinib would not have been expected if the first and second reasons are likely. One could speculate that docetaxel, a cytotoxic agent, would have some effect against the vast majority of the tumors, while gefitinib, a targeted agent, might be totally ineffective in patients not expressing the target. The differences in survival curves in the initial phase of follow-up might have reflected the effect of these 'relatively resistant' cases. Many patients, particularly from the docetaxel group, were actually crossed over to receive the other treatment. This made interpretation of the survival

Table 2 | Overall survival data (intent-to-treat analysis) from the V15-32 study

Study outcomes	Gefitinib	Docetaxel
Number of patients	245	244
Number of events	156	150
Median (range) survival time (months)	11.5 (9.8–14.0)	14.0 (11.7–16.5)
1-year survival (%)*	48	54
Response rate (%)	22.5	12.8

*Hazard ratio 1.12 (95% CI 0.89–1.40, $P = 0.330$); non-inferiority could not be demonstrated



Number of patients at risk:

Gefitinib	245	226	197	169	148	127	98	77	63	47	35	29	25	18	9	5	4	1	0
Docetaxel	244	233	214	189	173	140	105	87	69	44	35	25	18	14	10	7	6	3	0

Figure 2 | Table showing the overall survival data for patients treated in the randomized phase III V15-32 trial. Data courtesy of AstraZeneca.

results even more difficult. The decision to treat patients in the docetaxel arm with gefitinib as a post protocol therapy was probably on the basis of clinical information available; that is, patients with clinical features known to be favorable for the effect of gefitinib were selected. This selection criterion might have offset the survival benefit of gefitinib in the later phase of follow-up.[43]

On 1 February 2007, the Ministry of Health, Labour and Welfare examined the results of the V15-32 trial presented to the Drug Safety Policy Panel, Safety Policy Investigation Committee, and Second Food and Drug Advisory Board of 2006. The results of this meeting were published.[44] First, the safety policy on interstitial pneumonia described in the package insert concerning the adverse events of gefitinib is to be continued. Second, there is no evidence to support the preference of gefitinib over docetaxel for second-line or third-line treatment. Third, to evaluate the clinical efficacy of gefitinib, the difference in the survival curves in the V15-32 study should be analyzed in detail and detailed subset analyses must be conducted. Forth, clinical factors that might affect the drug effects, and the effect of *EGFR* mutations on drug responsiveness, must be evaluated.

Results of the INTEREST trial

The INTEREST trial was a randomized, open-label, parallel-group, phase III trial of gefitinib versus docetaxel in patients with locally advanced or metastatic and/or recurrent NSCLC with a previous history of platinum based chemotherapy.[17] The phase III study enrolled 1,466 patients from 149 centers in 24 countries. The primary end point was overall survival. The overall survival and 1-year survival rates were 7.6 months and 23%, respectively, in the gefitinib group. The corresponding survival rates were 8.0 months and 34%, respectively, in the docetaxel group. No significant differences in the outcomes between the two treatment arms were noted. The study demonstrated the noninferiority of gefitinib compared with docetaxel. Gefitinib was better tolerated, and the total outcome index of quality of life also favored gefitinib. On the basis of these data, AstraZeneca submitted a marketing authorization application to the European Medicines Agency for gefitinib as an agent for patients with locally advanced or metastatic NSCLC with a previous history of treatment with platinum-containing regimens. It is not known why the INTEREST trial demonstrated positive results, because the response rate to gefitinib is lower in Western patients compared with Japanese patients. The adjusted HR of gefitinib versus docetaxel in the V15-32 study was 1.01, which was almost identical to that in the INTEREST trial (HR = 1.02). This finding suggests that the efficacy of gefitinib was similar to that of docetaxel. Asian patients treated with docetaxel had a better outcome than Asian patients treated with gefitinib in the INTEREST trial. By contrast, Asian patients did not derive a benefit in the placebo arm in the ISEL trial. Since *EGFR* mutation was associated with better response to docetaxel in the INTEREST trial, it is possible that docetaxel worked better in the Asian patients, offsetting gefitinib efficacy in the comparisons and improving the overall outcomes of the Asian subset in the INTEREST and V15-32 studies.

Differences between TKIs and cytotoxic agents

Comparison of cytotoxic agents and molecular-targeted therapeutic drugs reveals that although the former show broader anticancer spectra, their maximal therapeutic quality in responders might be inferior compared with that of molecular-targeted therapeutic agents. Molecular-targeted agents can show narrow antitumor spectra but they can produce a profound effect. In general, the potency of the antitumor effect of the conventional cytotoxic agents is likely to be greater when clinical trials are conducted on large numbers of patients. Molecular-targeted agents exhibit antitumor activity only in those cells that possess the relevant molecular target, hence the effects of these drugs on overall tumor volume reduction would be lower than that of the conventional cytotoxic agents, even when both exert the same response rate.

Thus, the survival rate of patients treated with the molecular-targeted agents might not improve, even if the response rate is twice that of the conventional cytotoxic agents. The results of the V15-32 study indicate

this possibility. Waterfall plot figures have been used frequently for evaluation of the antitumor activities of drugs. The rates of variability in the responses of the tumors of each patient are plotted. If the value is positive the tumor is judged to have increased in size, and if the value is negative the tumor is judged to have reduced in size. The number of patients experiencing even the slightest tumor reduction is often expressed as a percentage. Waterfall plots have been suggested to be suitable for evaluation of the effects of cytotoxic antineoplastic agents against malignant tumors because they suppress tumor growth regardless of the molecular target of each agent. RECIST (Response Evaluation Criteria in Solid Tumors), commonly used all over the world for drug evaluation, have been introduced because it is impossible to measure the size of each tumor accurately. It would be unreasonable to expect highly reliable results from Waterfall plots, as it is not possible to measure tumor size accurately. These plots perhaps suffer from over or underestimation of the effects of drugs. There are occasional reports of analysis of the effects of molecular-targeted agents by the use of Waterfall plots. It has been suggested that cases demonstrating reduction of tumor size can be clearly separated from those not showing a size reduction in the evaluation of the antitumor effects of molecular-targeted drugs, because molecular-targeted drugs are effective only against tumors with expression of the molecular target (Figure 4). If we view the results of V15-32 with this information in mind, it is probable that the magnitude of the antitumor activity of docetaxel overall would be greater than that of gefitinib, which shows significant effect only in a small number or specific subsets of patients. In particular, it would be anticipated that differences in the antitumor activities between conventional cytotoxic agents and molecular targeted agents would be marked in those patients who do not express the molecular targets.

Patients that may benefit from gefitinib

The high degree of sensitivity to gefitinib of NSCLCs that harbor *EGFR* mutations has been demonstrated in a prospective phase II study: the response rate to gefitinib was about 80%, and both progression-free survival and overall survival were prolonged.[24,25] NSCLC with *EGFR* mutations has also been suggested to be highly sensitive to cytotoxic antineoplastic agents, and it would be necessary to establish the superiority of gefitinib through comparative studies in this group of patients. It is unknown whether gefitinib should be the preferred drug in patients with tumors carrying *EGFR* mutations. According to a report from the National Cancer Center Central Hospital in Japan, the efficacy rates of gefitinib in those with *EGFR* mutations is 82% compared with only 11% in those without such mutations. Thus, the decision to employ gefitinib on the basis of the presence of *EGFR* mutations in the tumors would be incorrect—possibly in as many as 10–20% of the patients.[26] Moreover, determination of the presence of *EGFR* mutations is possible in only 25% of patients with advanced lung cancer, which

Figure 3 | Retrospective analysis of the survival data from the randomized phase III V15-32 trial. Permission obtained from Takeuchi & Takeuchi, M. *J. Lung Cancer* **7**, 1–8 (2007)

poses a problem in selecting the most appropriate treatment.[7] The problem could be resolved if the methodology for the detection of *EGFR* mutations could be improved. It is known that progression-free survival and overall survival end points are favorable among patients who are Asian, are female, have adenocarcinoma histology and are nonsmokers, but the number of patients who meet all of these criteria is limited. Furthermore, when a group of patients who meet at least one of these criteria is selected, the incidence of false-positive and false-negative responses will increase. The results of the V15-32 study suggest that gefitinib should be administered as the drug of first choice only to patients with clear-cut targets, but currently there are no methods to distinguish these patients in a reliable manner.

Results of the IPASS trial

IPASS (IRESSA Pan Asia Study) was a phase III study designed to compare oral gefitinib monotherapy with intravenous carboplatin and paclitaxel chemotherapy as first-line treatment in chemotherapy-naive Asian patients with advanced NSCLC.[27] The eligibility criteria were: age ≥18 years, life expectancy ≥12 weeks, adenocarcinoma histology, never-smokers or light ex-smokers, performance status 0–2, stage IIIB/IV, and presence of measurable disease. A total of 1,217 patients were recruited between March 2006 and October 2007 from nine Asian countries, including China, Japan, Thailand, Taiwan, Indonesia, Malaysia, Philippines, Hong Kong and Singapore. Patients were randomly assigned to receive either 250 mg daily gefitinib ($n = 609$) or carboplatin (AUC 5 or 6) and paclitaxel (200 mg/m^2) ($n = 608$). The primary end point was noninferiority of these two arms for progression-free survival. The secondary end points were overall survival, objective response rate, quality of life, symptomatic improvement, and toxicity. Association of the efficacy with EGFR biomarkers was also analyzed as an exploratory end point. The study exceeded its primary end point and demonstrated the

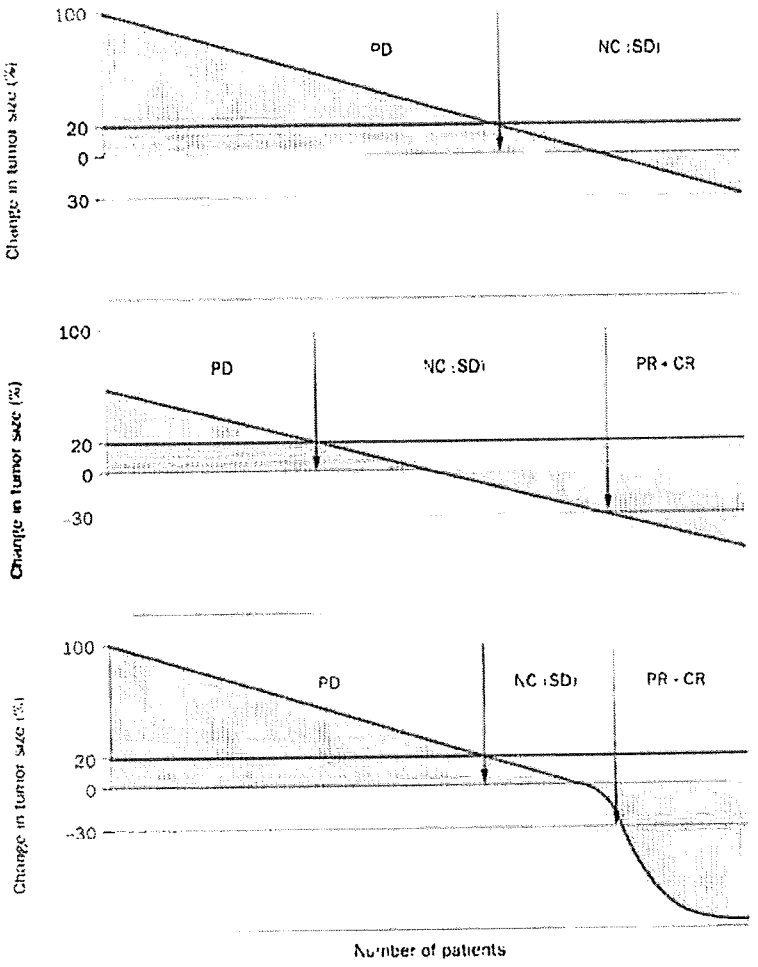


Figure 4 | Waterfall plots showing the differences in the effect of cytotoxic drugs and molecular-target drugs on tumor size. Abbreviations: CR, complete response; NC, no change; PD, progressive disease; PR, partial response; SD, standard deviation. Permission obtained from Takeuchi © Takeuchi, M. *J. Lung Cancer* 7, 1–8 (2007)

superiority of gefitinib over carboplatin and paclitaxel, in terms of progression-free survival, in the first-line setting. The risk of overall progression was reduced by 26% in gefitinib-treated patients compared with those who were administered chemotherapy.[14]

Interestingly, the treatment effect was not constant over time. The progression-free survival curves crossed at 6 months, favoring carboplatin and paclitaxel during the first 6 months and gefitinib thereafter. This evidence suggested there were two different populations of patients with regard to response to the chemotherapy doublet and gefitinib. In exploratory biomarker analyses, the progression-free survival was longer for patients with *EGFR* mutations who received gefitinib, compared to chemotherapy. By contrast, progression-free survival was longer for those in the carboplatin and paclitaxel arm than the gefitinib arm in patients with wild-type *EGFR*. A similar trend was observed in the exploratory analyses based on the *EGFR* copy number status. The target population in the IPASS trials was selected on the basis of clinical characteristics, such as presence or absence of adenocarcinoma histology and smoking history. About 60% of the patients had *EGFR* mutations in the tumor cells. In the 40% of patients without *EGFR* mutations, gefitinib showed no beneficial effect, whereas chemotherapy was effective. This is why the progression-free survival curves in the IPASS study crossed at 6 months after the start of treatment. The response rate to both gefitinib and chemotherapy was higher in those with *EGFR* mutations compared with those without such mutations; however, gefitinib had a greater beneficial effect than chemotherapy in patients with *EGFR* mutations. Another important finding of the IPASS trial was the extremely low response rate to gefitinib in patients with wild-type *EGFR*. The method used for the detection of these mutations was very sensitive, namely the scorpion ARMS method, so that all the mutation-positive patients could be identified. The overall survival data from the IPASS trial are awaited; however, the results of the IPASS trial have demonstrated that molecular-targeted drugs are effective only against tumors with the relevant molecular target, that is, *EGFR* mutations. Conversely, cytotoxic drugs have antitumor activity against tumors regardless of the presence or absence of *EGFR* mutations.

Lessons learned from EGFR-TKI data

Gefitinib has shown dramatic antitumor activity in phase I and II trials. As second-line treatment for Japanese patients with NSCLC, it produced response rates of almost 30%. In a placebo-controlled, comparative trial (ISEL)[15] the effect of gefitinib as second-line and third-line treatment for NSCLC in prolonging survival was proven among Asians, as demonstrated by the high response rates in the predefined subgroup analysis. By contrast, in non-Asians with low response rates, the survival curves of those treated with gefitinib versus no treatment were almost entirely superimposed. Paradoxically, in the BR-21 trial, the overall survival of patients treated with the EGFR-TKI, erlotinib, was significantly better than that of patients administered placebo, despite the low response rate.[16] In the subset analysis of BR-21, the efficacy of erlotinib in terms of survival benefit was reported to be observed in male patients or those with squamous histology, although these factors were associated with lower response rate. One could speculate that erlotinib might be effective in patients with wild-type *EGFR* tumors, although not to the extent to achieve major shrinkage of the tumor. If so, erlotinib could be regarded as a 'less-targeted drug' than gefitinib, since its efficacy is less affected by the target status of the tumor. Dosing strategies of gefitinib (administered at a third of the maximum tolerated dose) and erlotinib (administered at the maximum tolerated dose) are different, which could partly account for the discrepancy. This explanation should be tested in future clinical trials.

Four large, randomized trials, namely Intact 1 and 2, Talent, and Tribute, that compared the effect of a platinum doublet regimen with or without gefitinib or erlotinib yielded negative survival results, probably because of the limited effect of gefitinib or erlotinib.[17,18] The patients

accrued to these trials were not selected according to their *EGFR* mutational status or EGFR histology, smoking and gender status. Another reason might be a competitive cell cycle effect of anticancer agents and molecular-targeted drugs. Two randomized, controlled trials, namely V15-32 and INTEREST, that compared gefitinib with docetaxel for second-line or third-line treatment NSCLC have been reported.[31,35] Although theV15-32 study did not demonstrate the noninferiority of gefitinib, the INTEREST trial established the noninferiority of this agent despite the low response rate observed in Western patients. It has long been believed that response is a good surrogate for progression-free survival or overall survival. The results of the V15-32 study do not support this hypothesis, and this finding poses a challenge when comparing the effect of molecular-targeted agents with that of cytotoxic antineoplastic agents on the basis of end points such as progression-free survival and overall survival.

The high response rate in the IPASS trial reflected the good progression-free survival for those treated with gefitinib. However, the progression-free survival curves crossed after 6 months, which suggests the existence of two different populations of patients with different effects of molecular-targeted drugs between the two groups. The IPASS trial was a clinical trial in a partially selected population of patients, which suggests the need for more-accurate selection of patients in future clinical trials. Nevertheless, results of the IPASS trial will have some influence on the interpretation of results of ongoing clinical trials. Comparative trials of gefitinib and platinum-based doublets for patients with advanced and/or recurrent disease who harbor *EGFR* mutations will need to be modified as it might be difficult to obtain informed consent from these populations, owing to the finding that progression-free survival is significantly longer in patients treated with gefitinib than in those receiving platinum-based chemotherapy.

Another issue relates to the antitumor activity of cytotoxic drugs against tumors with *EGFR* mutations. In the V15-32 trial, progression-free survival was better in patients with *EGFR* mutations who were treated with either gefitinib or chemotherapy. In the IPASS trial, progression-free survival in those who received gefitinib was quite different between patients with and without *EGFR* mutations. Conversely, progression-free survival tended to be better in patients with *EGFR* mutations than in those without such mutations who were administered platinum-based chemotherapy, although this difference was not significant despite the response rate to platinum-based chemotherapy being significantly higher in patients with *EGFR* mutations. The presence of *EGFR* mutations in the tumor is a predictive factor of response not only to EGFR-TKIs, but also to platinum-based chemotherapy. Thus, the role of *EGFR* mutations as a predictive factor of progression-free survival and overall survival remains unclear in patients treated with platinum-based chemotherapy. Although many randomized trials of EGFR-TKIs in unselected patients with NSCLC have been reported, the results are varied and it is quite difficult to interpret the outcomes of these clinical trials.[7–9]

Conclusions

The results of several randomized, controlled trials of targeted agents and cytotoxic therapies in patients with advanced NSCLC have produced confusing results, perhaps because of the following reasons. First, the modes of action of cytotoxic drugs and molecular-targeted drugs are different, although the differences remain to be precisely elucidated. Second, the majority of clinical trials have been conducted in unselected populations. The IPASS trial was conducted in a partially selected population; however, the additional analysis on the basis of *EGFR* mutations clearly identified the target populations that show response to EGFR-TKI and cytotoxic chemotherapy. Third, although biomarker studies are extremely important, the majority of biomarkers have not been validated and the techniques to assess the EGFR target have not been fully optimized. Data from classical biomarker studies might not be the best data to draw conclusions from because these studies were conducted without selecting patients on the basis of favorable profiles. For the field of personalized medicine with the use of targeted and cytotoxic agents to advance, the scientific and clinical significance of biomarkers should be analyzed more extensively.

Review criteria

Data for this Review were obtained by searching the PubMed database for articles published between 1 January 2000 to 1 November 2008. Only articles published in English were considered. The following search terms were used "non-small-cell lung cancer" "NSCLC", "epidermal growth factor receptor" "EGFR" and "tyrosine kinase inhibitor". When possible primary sources have been cited. Data from searches of the following conferences were also included: ASCO 2004–ASCO 2008 annual meetings, European Society of Medical Oncology 2008 annual meeting, and the 12th World Conference on Lung Cancer 2007.

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Original Article

A Phase I Study of Gemcitabine and Carboplatin in Patients with Advanced Non-small Cell Lung Cancer and a Performance Status of 2

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Objective: The aim of this study was to determine the maximum-tolerated dose (MTD) and the recommended dose of combination chemotherapy with gemcitabine (GEM) and carboplatin (CBDCA) in non-small cell lung cancer (NSCLC) patients with a performance status (PS) of 2.

Methods: Chemotherapy-naïve NSCLC patients with PS 2 were enrolled. Chemotherapy consisted of an escalated dose of GEM on days 1 and 8 and CBDCA on day 1 every 3 weeks. Patients were scheduled to receive GEM (mg/m^2)/CBDCA (area under the curve: AUC) at four dose levels: 800/4 (level 1), 1000/4 (level 2), 1000/4.5 (level 3) and 1000/5 (level 4), respectively.

Results: Between February 2004 and August 2006, 13 patients were enrolled in this study. Dose-limiting toxicities (DLTs) were thrombocytopenia, febrile neutropenia and hyponatremia. DLTs were observed in two of six patients at dose level 1 and in three of six patients at dose level 2. Dose level 2 was thus determined to be the MTD. Among 12 evaluable patients, 7 patients had stable diseases and 5 patients had progressive diseases, and the median survival time was 3.8 months.

Conclusions: The MTD and the recommended dose for Phase II studies of this regimen were determined to be GEM 1000 mg/m^2 and CBDCA AUC of 4. Additional objective measures are needed to evaluate patients' risk and benefit in future clinical trials for PS 2 patients.

Key words: non-small cell lung cancer – performance status 2 – gemcitabine – carboplatin – Phase I

INTRODUCTION

Platinum-based combination chemotherapy has been shown to improve survival and quality-of-life (QOL) in patients with advanced non-small cell lung cancer (NSCLC) (1,2). In the 1990s, new chemotherapeutic agents, such as gemcitabine (GEM), vinorelbine, docetaxel, paclitaxel (PTX) and irinotecan, were developed. Currently, platinum-based chemotherapy employing these new agents is accepted as the standard chemotherapy worldwide (3,4). In addition, a meta-analysis demonstrated significant longer progression-free survival of GEM and platinum combination compared with other new agents and platinum combinations (5). Thus, combination chemotherapy with GEM and platinum is now considered as one of the most active regimens for advanced NSCLC.

Like in other types of cancers, performance status (PS) has been shown to be one of the most important prognostic factors for survival in advanced NSCLC (6–8). Patients with

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impaired PS generally have lower response rate and shorter survival in spite of high risk for severe toxicities (9,10). Historically, clinical trials have excluded patients with Eastern Cooperative Oncology Group (ECOG) PS of 2 or worse. To date, it has not been fully elucidated whether platinum-based combination chemotherapy is feasible and effective in patients with PS 2.

Carboplatin (CBDCA), an analog of cisplatin (CDDP), has lower nephro- and gastrointestinal toxicity and has been widely used as a substitution of CDDP. Several randomized trials have shown the equivalence between GEM + CBDCA (GC) and GEM + CDDP (GP) in terms of response rate and survival (11,12). In those trials, toxicities, such as emesis, nephropathy and neuropathy were significantly mild in GC. Although recent meta-analysis disclosed slightly but significant survival advantage of CDDP (13,14), GC can be one of the treatment options, especially for patients who are not suitable to receive CDDP. In a randomized Phase III trial comparing GC with vinblastine + CDDP, GC showed better response rate and survival, and toxicities were similar between the two arms (15). Although 70% of all enrolled patients in the study had PS 2, overall response rate and median survival time (MST) were 27% and 11.6 months in GC arm. These survival data were comparable to those in patients with PS 0 or 1 who treated with platinum-based chemotherapy.

These results suggest the potential benefit of GC in patients with PS 2; however, the optimal dose of GC has not been investigated in patients with impaired PS. Therefore, we conducted a Phase I study to determine the maximum-tolerated dose (MTD) and the recommended dose for Phase II studies of GC in advanced NSCLC patients with PS 2.

PATIENTS AND METHODS

Eligibility

Patients with histologically or cytologically proven advanced NSCLC were eligible for the study. Each patient was required to meet the following criteria: (i) clinical stage IIIB or IV; (ii) ECOG PS of 2; (iii) aged 20–75 years; (iv) measurable lesion; (v) no prior chemotherapy; (vi) adequate hematological function (white blood cell $\geq 3500/mm^3$, hemoglobin ≥ 9.5 g/dl and platelets $\geq 100\,000/mm^3$); (vii) adequate hepatic and renal function (total bilirubin ≤ 1.5 mg/dl, AST and ALT < 100 IU/l and creatinine ≤ 1.5 mg/dl); (viii) $PaO_2 \geq 60$ mmHg; and (ix) written informed consent. Patients with active concomitant malignancy, radiologically apparent interstitial pneumonia or pulmonary fibrosis, serious concurrent illness (e.g. uncontrolled diabetes mellitus, hypertension, angina pectoris, myocardial infarction within 3 months after onset or severe infection), history of severe drug allergy or pregnant/lactating women were excluded. The study protocol was approved by the institutional review board of the National Cancer Center.

Treatment Schedule

This was a Phase I, dose-escalation study planned for GEM on days 1 and 8 and CBDCA on day 1 of a 21-day course. The initial dose level of GEM was 800 mg/m^2 and CBDCA was an area under the concentration–time curve (AUC) of 4 mg min/ml. The actual dose of CBDCA was calculated based on Cockcroft–Gault equation (16) and Calvert formula (17) every course. CBDCA was infused over 60 min, and 60 min after the completion of CBDCA infusion, GEM was administered over 30 min. Prophylactic administration of granulocyte colony-stimulating factor (G-CSF) was not permitted. Administration of G-CSF was permitted for patients with grade 4 neutropenia and/or leukopenia and grade 3 febrile neutropenia. The administration of GEM was omitted on day 8 if patients met one of the following criteria: white blood cell $<2000/mm^3$, neutrophil $<1000/mm^3$, platelets $<50\,000/mm^3$ and PS ≥ 3. No dose modification of GEM was permitted on day 8. If dose-limiting toxicity (DLT) was observed, the dose of each drug was reduced to 80% in the next course of chemotherapy. Treatment was to be performed for at least two courses, unless unacceptable toxicity or disease progression occurred.

The DLT was defined as follows: grade 4 thrombocytopenia, grade 3 or grade 4 febrile neutropenia, grade 3 non-hematological toxicity (except for nausea/vomiting and alopecia) and omission of the treatment on day 8. Dose-escalation schedule is shown in Table 1. Initially, three patients were treated at each dose level. If DLT was not observed in any of three patients, dose escalation was made. If DLT was observed in one or two of three patients, an additional three patients were entered in the same dose level. If DLT was observed in three or more of six patients or all of the initial three patients, we considered that the dose was the MTD. If DLT was observed in one or two of six patients, dose escalation was also made. Dose escalation was decided by the toxic data only in the first course of chemotherapy.

Baseline and Treatment Assessment

Pre-treatment evaluation consisted of complete medical history and physical examination, complete blood cell counts, blood chemistry studies, electrocardiograph, arterial blood gas analysis, chest radiography, computed tomography (CT) of the chest, CT or ultrasound study of the abdomen,

Table 1. Dose-escalation schedule

Dose level	Gemcitabine (mg/m^2)	Carboplatin (AUC)	No. of patients
1	800	4	3–6
2	1000	4	3–6
3	1000	4.5	3–6
4	1000	5	3–6

AUC, area under the curve.