and the added possibility of direct antitumor activity [4, 5]. More recently, there has been accumulating phase III evidence that concomitant chemoradiotherapy probably yields higher response rates and survival in patients with stage III disease [7, 8].

Several novel agents with remarkable radiosensitizing properties have recently been introduced in clinical practice. In preclinical studies the taxanes were found to be potent radiation-enhancers by virtue of their ability to cause cell cycle arrest in the radiosensitive G2/M phase [9, 10]. Preclinical studies further illustrated the taxanes' radiosensitizing effect in tumor-cell lines, with docetaxel exhibiting an effect ten times that of paclitaxel at equimolar concentrations [11]. Four phase I trials of docetaxel and concurrent radiation have been reported [12–15]. Mauer et al. [12] and Koukourakis et al. [14] conducted phase I trials of weekly docetaxel with concurrent thoracic radiotherapy and determined that the maximum-tolerated dose (MTD) of weekly docetaxel was 20–30 mg/m^2 with thoracic radiation. The dose-limiting toxicities (DLTs) were esophagitis and neutropenia. The phase II studies of docetaxel [16, 17] and thoracic radiotherapy have shown an encouraging, high response, but an increased incidence of esophagitis and asthenia was observed.

The use of low daily doses of cisplatin concomitantly with RT seems to be of particular interest, since clear synergism has been demonstrated in vitro [18]. In a European Organization for Research and Treatment of Cancer (EORTC) study, daily administration of cisplatin proved to be more effective than a weekly schedule in potentiating the local tumor control achievable with RT alone, although the difference between the two schedules were not statistically significant [4].

In view of these considerations, we planned this phase I study. The objectives of this study were to determine the MTD, recommended dose (RD) and DLT of cisplatin and docetaxel when given weekly concomitantly with conventional TRT, and evaluate the efficacy of this regimen.

Moreover, since it has reported that serum α-1-acid glycoprotein (AAG) combined with docetaxel extensively [19] and that the AAG levels were significantly associated with time to progression in NSCLC patients and febrile neutropenia [20]. The AAG levels were significantly associated with the toxicity of docetaxel because AAG strongly binds docetaxel in serum. Thus, we examined the relationship between serum AAG level and major toxicities in this regimen.

Patients and methods

Patient eligibility

Previously untreated patients with histologically or cytologically documented inoperable stage IIIA or IIIB NSCLC were eligible for this study. Patients with malignant pleural effusion or any disease that required irradiation of more than half of the hemithorax were ineligible. Other eligibility criteria included: (1) age less than 75, (2) Eastern Cooperative Oncology Group performance status equal to or less than 2, (3) evaluable or measurable disease, (4) no prior therapy, (5) adequate bone marrow function (leukocyte count ≥4,000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥9.5 g/dl), renal function (serum creatinine ≤ 2.0 mg/dl), hepatic function (AST/ALT ≤ 2.5 times upper limit of normal, serum bilirubin ≤ 1.5 mg/dl), and pulmonary function (arterial blood gases PaO2 ≥70 mmHg), (6) absence of active infection, heart failure, or acute myocardial infarction within 3 months before study entry, no serious medical or psychiatric illness. All patients signed an informed consent form that was approved by each of the institutional review boards. Before entry into the study, all patients underwent an evaluation that consisted of a complete history and physical examination, chest X-ray, chest and upper abdomen (to include the liver and adrenals) computed tomography (CT) scan, brain CT or MRI, and a bone scan.

Chemotherapy

The treatment regimens are outlined in Fig. 1. The study was designed to fix the cisplatin dose at 25 mg/m^2/week and escalate docetaxel dose. The docetaxel and cisplatin administration schedules were: split schedule (SS), 3 out of every 4 weeks (day 1, 8, 15, 29, 36, and 43), continuous schedule (CS), weekly (day 1, 8, 15, 22, 29, 36). Docetaxel was administered as an intravenous (IV) infusion over 30 min and followed by cisplatin given as an IV infusion over 30 min. The participating investigators at each institution were allowed to decide the volume of fluid replacement and the antiemetic therapy to be administered, but adequate amounts of parenteral fluid and diuretics were given in order to prevent the renal toxicity of cisplatin. The patients did not receive steroids due to prevention of a hypersensitivity reaction. The starting dose of docetaxel was 20 mg/m^2/week, and the docetaxel dose was increased by 5 mg/m^2/week. There was no dose escalation in individual patients, and administration of cisplatin and docetaxel was cancelled if the leukocyte count fell below 2,000/mm^3 or any DLTs occurred.

At first, we planed only sequential schedule. However, as we thought that continuous schedule had a stronger radiosensitizing effect compared with sequential schedule, we amended protocol and added continuous schedule. After the MTD and RD of SS had been determined, we treated with CS using the RD of SS.

Thoracic radiation

Thoracic radiation therapy of 60 Gy in 2.0 Gy fractions was given concurrently with weekly docetaxel and

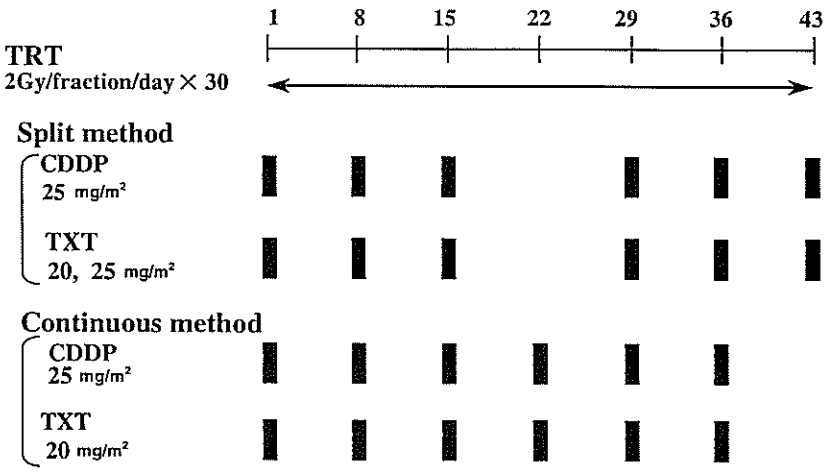

Fig. 1 Treatment regimens for weekly docetaxel and cisplatin concomitant with TRT

cisplatin infusion for 6 weeks. A 6- or 10-MV linear accelerator was used. Two-dimensional treatment planning of TRT was performed by conventional X-ray simulators. Inhomogeneity correction for lung tissues was not done. The initial planning target volume (PTV) consisted of the primary tumor, ipsilateral hilar nodes, and superior mediastinal nodes with 1–1.5 cm margin. If metastasis to supraclavicular nodes were found, they were also included in the initial PTV. This initial large field was treated by parallel-opposed anterior and posterior fields to 40 Gy in 20 fractions. The widths and lengths of the initial fields with appropriate trimming ranged from 10.5 to 16 cm (median; 14 cm) and 10.5–20 cm (median; 16 cm), respectively. After 40 Gy, oblique parallel-opposed fields were used to exclude the spinal cord. The angles of the oblique fields ranged from 15° to 45° with a median of 40°. In the boost fields, the primary tumors and the involved nodes were included with a margin of 0.5–1.5 cm. The total dose to the boost field was 60 Gy in 30 fractions. In the present study, patients were excluded if the initial radiation field exceeded half of the ipsilateral lung. However, no dose constraints on the normal tissues including the percentage of pulmonary volume irradiated to > 20 Gy (V20) or esophageal length was determined, as three-dimensional treatment planning using a CT-simulator was not available.

If grade 4 hematologic toxicity occurred during the course of TRT, it was suspended and restarted after recovery to grade 3 or less. If grade 3 or greater esophagitis occurred and the physician decided that the TRT could not be continued, it was suspended and restarted after recovery to grade 2 or less. If PaO_2 fell to 10 torr and a patient had a fever of 38°C or higher, both TRT and chemotherapy were suspended and restarted immediately after recovery.

Definition of MTD, RD and DLT

Maximum-tolerated dose was defined as the dose level at which DLT occurs in more than 50% of the patients treated, and the preceding dose level was defined as RD. At least six patients were entered at each dose level. DLT was defined as grade 4 leukopenia or neutropenia lasting 3 days or more, a platelet count of ≤ 20,000/mm^3, febrile neutropenia and grade 3 or greater non-hematologic toxicities other than nausea and vomiting. Suspension of docetaxel and cisplatin two or more times was also considered as a DLT.

Response evaluation and survival analysis

The criteria for assessing the response to treatment were as follows. Complete response (CR) was defined as total disappearance of all clinically detectable lesions for at least 4 weeks. Partial response (PR) was defined as a reduction of 50% or more in the sum of the products of the cross-sectional diameters of all measurable lesions for at least 4 weeks, without the development of new lesions. Stable disease (SD) was defined as a reduction of less than 50% or an increase of less than 25% in the sum of the products of the cross-sectional diameters of all measurable lesions, with no clear evidence of either regression or progression for at least 6 weeks. Progressive disease (PD) was defined as an increase of 25% or more 25% in the sum of the products of the cross-sectional diameters of all measurable lesions, together with an increase of assessable disease or the appearance of new lesions. Survival time was defined as the interval between the date of the start of treatment and the date of death due to any cause or the most recent follow-up evaluation. The survival curves were estimated by the Kaplan–Meier method.

Statistical analysis

The *T*-test was used to examine the relationship between serum AAG values and the categorical endpoints of major toxicities, such as grade of esophagitis. A *P*-value of 0.05 or less was considered statistically significant.

Results

Patient characteristics

Between April 1999 and April 2000, 21 patients were enrolled in the study, and their characteristics are listed in Table 1. All patients were eligible for evaluation of efficacy, but one who enrolled at a docetaxel dose of 20 mg/m^2/week in SS was excluded from the evaluation of toxicity because chemotherapy was suspended due to exacerbation of a gastric ulcer. That patient experienced no DLT. The 19 men and 2 women enrolled in the study had a median age of 65 (range: 51–75). Most patients had squamous cell carcinoma ($n=16$: 76%) and stage IIIB disease (n = 17: 81%). Median performance status was 1 (range: 0–2), while only two patients had a performance status of 2.

Dose escalation

The DLTs encountered at each dose level are listed in Table 2. On the SS, six and seven patients were evaluable for toxicity at docetaxel doses of 20 and 25 mg/m^2/week, respectively. Two of the six patients at the 20 mg/m^2/week dose experienced DLTs consisting of grade 3 esophagitis in one patient and cancellation of chemotherapy twice because of grade 3 leukopenia in the other. At the 25 mg/m^2/week dose, four of the seven patients developed DLTs consisting of grade 3 esophagitis in two patients, grade 3 fatigue in one, and febrile neutropenia in one. Accordingly, the MTD and RD on the SS were concluded to be a dose of docetaxel 25 and 20 mg/m^2/week, respectively. The next cohort of patients was treated with a docetaxel dose of 20 mg/m^2/week in CS. However, four of the seven patients developed DLTs, consisting of grade 3 esophagitis in two patients, grade 3 fatigue in one patient, and cancellation of chemotherapy twice because of grade 3 neutropenia in one patient. Finally, we concluded that the dose level 1 in SS was the recommended dose for further study of this therapy.

Table 1 Patient characteristics

Characteristic	Number of patients
Total number of patients	21
Assessable for toxicity	20
Assessable for survival and response	21
Age, years	
Median (range)	65 (51–75)
Sex	
Male	19
Female	2
Performance status	
0	6
1	13
2	2
Histology	
Squamous cell carcinoma	16
Adenocarcinoma	5
Stage	
IIIA	4
IIIB	17

Toxicity

Hematologic and non-hematologic toxicities are summarized in Table. 3 and 4. Twenty patients could be assessed for toxicities. The hematologic toxicities were mild, and there were no grade 4 hematologic toxicities. Grade 3 neutropenia, decrease in hemoglobin, and thrombocytopenia were observed in 6 patients (30%), 6 patients (30%), and 1 patient (5%), respectively. Febrile neutropenia developed in only one patient, and it occurred at the 25 mg/m^2/week dose of docetaxel.

The principal toxicity on this regimen was esophagitis. Grade 2 or higher esophagitis occurred in 12 of the 20 (60%) patients enrolled, and in 5 cases (25%) it was of grade 3 and caused suspension of treatment in 2 patients and permanent discontinuation of treatment in one patient at 52 Gy. Another dose-limiting non-hematologic toxicity was grade 3 fatigue which occurred in one patient each at 25 mg/m^2/week dose of docetaxel on the SS and at the 20 mg/m^2/week dose of docetaxel on the CS. Other non-hematologic toxicities were mild and never greater than grade 2. Grade 2 nausea and pneumonitis occurred in five patients and two patients, respectively. No hypersensitivity reactions occurred. There were no treatment related deaths.

Treatment delivery

A total of 110 chemotherapy cycles were administered to 20 patients at three dose levels. Ten (9%) of the planned doses were omitted. The ratio of actual dose intensity to planned dose intensity of docetaxel and cisplatin at 20 and 25 mg/m^2/week docetaxel dose levels on the SS and at the 20 mg/m^2/week docetaxel dose level on the CS was 0.95, 0.93, and 0.88, respectively. A TRT dose of 60 Gy was administered to 18 of 20 (90 %) patients. TRT at the 25 mg/m^2/week dose of docetaxel on the SS and the 20 mg/m^2/week of docetaxel on the CS each one patient was discontinued at 58 and 52 Gy, respectively, because of grade 3 esophagitis.

Response and survival

Table 5 shows the responses observed at each dose level. All 21 patients enrolled were evaluable for response. CR was observed in 5 of the 21 (24%) patients, PR in 14 (67%) and SD in 1 (5%). The overall response rate was 90% (95% confidence interval: 69.6–98.8%). No significant differences in response were observed between the three dose levels of docetaxel.

Table 2 Dose limiting toxicity

Dose of docetaxel	Assessable patients	Dose limiting toxicitiy	
Split schedule			
20 mg/m^2	6	2	1: Grade 3 esophagitis1: 2 times cancellation of chemotherapy due to grade 3 leukopenia
25 mg/m^2	7	4	2: Grade 3 esophagitis1: Grade 3 fatigue1: Febrile neutropenia
Continuous schedule			
20 mg/m^2	7	4	2: Grade 3 esophagitis1: Grade 3 fatigue1: 2 times cancellation of chemotherapy due to grade 3 neutropenia

Table 3 Hematologic toxicity

Dose level of docetaxel	No. of patients	ANC		Febrile neutropenia	Hb		Platelet	
		Grade			Grade		Grade	
		3	4		2	3	2	3
Split schedule								
20 mg/m^2	6	0	0	0	1	2	0	0
25 mg/m^2	7	2	0	1	3	2	1	1
Continuous schedule								
20 mg/m^2	7	4	0	0	2	2	0	0

ANC absolute neutrophil count, *Hb* hemoglobin

Figure 2 shows the overall survival for all 21 patients enrolled in the study; 16 patients (76%) had died at the time of the analysis. All survivors had a follow-up time of 30 months. Based on the Kaplan–Meier method, the 1-, 2-, and 3-year overall estimated survival rates were 71.4, 42.9, and 32.7%, respectively. The median overall survival time was 23.1 months.

Relationship between esophagitis and plasma AAG levels

The principle toxicity on this regimen was esophagitis. Another DLT, grade 3 fatigue occurred in only two patients, and hematologic toxicity was mild. We, therefore, examined the relationship between plasma AAG levels and grade of esophagitis. Plasma AAG was measured in 12 patients prior to the start of the treatment, and the baseline AAG level of the patients who experienced grade 2 or 3 esophagitis was significantly higher ($P=0.04$) than that of the patients who experienced grade 0 or 1 esophagitis (grade 0/1, mean AAG level = 168 pg/ml vs. grade 2/3, mean AAG level = 83 pg/ml: Fig. 3).

Discussion

We conducted a phase I study of cisplatin and docetaxel administered in weekly infusions concomitant with conventional TRT in patients with unresectable stage IIIA/IIIB NSCLC. This is the first study that examined schedule and dose of weekly docetaxel in combination fixed dose of cisplatin 25 mg/m^2 concomitant with TRT. The recommended dose and schedule were determined to be cisplatin 25 mg/m^2 and docetaxel 20 mg/m^2 on days 1, 8, 15 of every 4 weeks, respectively. Esophagitis and neutropenia were by far the severest toxicities in this

Table 4 Non-hematologic toxicity

Dose level of docetaxel	No. of patients	Esophagitis		Fatigue		Nausea		Pneumonitis	
		Grade		Grade		Grade		Grade	
		2	3	2	3	2	3	2	3
Split schedule									
20 mg/m^2	6	3	1	0	0	2	0	1	0
25 mg/m^2	7	1	2	0	1	1	0	1	0
Continuous schedule									
20 mg/m^2	7	3	2	1	1	2	0	0	0

Table 5 Response at each dose level

Dose level of docetaxel	No. of patients	Response				Response rate
		CR	PR	SD	PD	
Split schedule						
20 mg/m^2	7	2	5	0	0	7/7100%
25 mg/m^2	7	2	5	0	0	7/7100%
Continuous schedule						
20 mg/m^2	7	1	4	1	0	5/771%
Total	21	5	14	1	1	19/2190%

study, while pulmonary toxicity was almost nonexistent. The pulmonary toxicity associated with concurrent chemoradiotherapy using third generation anticancer agents is frequently serious and fatal. When cisplatin and paclitaxel were combined with concurrent TRT, grade 3 or more late lung toxicity in 20%, including grade 5 in 8% was reported [21]. The incidence of grade 3 or more pulmonary toxicity in the studies of cisplatin and docetaxel concomitant with TRT has been low. Grade 3 pneumonitis occurred in 4.8% of patients in the study by Kiura et al. [22], and no grade 3 or more pulmonary toxicity was reported by Wu et al. [23].

Wu et al. [23] conducted a phase I study of weekly docetaxel and cisplatin concomitant with thoracic radiotherapy in stage III NSCLC and reported that the recommended dose was docetaxel 20 mg/m^2 plus cisplatin 20 mg/m^2 weekly. This dose is almost the same as in our study, but the dose intensity of docetaxel at the recommended dose was slightly lower in our study (docetaxel: 14 mg/m^2/week) than in the Wu study (docetaxel: 20 mg/m^2/week). The reason for this difference may be the dose of cisplatin.

Unfortunately, three-dimensional treatment planning and conformal radiotherapy were not available in the present study. Therefore, it was not possible to analyze a relationship between degree and frequency of toxicities and various dose-volume parameters including V20 or the maximum esophageal point dose. The acute toxicities are closely related to the dose-volume parameters of the normal tissues [24–26]. The degree and frequency of toxicities could be reduced by three-dimensional conformal radiation therapy, which can restrict the dose and volume of the normal tissues compared with conventional two-dimensional technique.

The response rate of 90%, median survival time of 23.1 months, and 2-year survival time of 42.9% obtained in our study are very encouraging. One reason for these favorable results may be that the weekly docetaxel and cisplatin not has only radiosensitizing activity but systemic chemotherapeutic activity. Ohe et al. [27] are currently evaluating docetaxel and cisplatin administered in three consecutive weekly infusions as systemic chemotherapy for advanced NSCLC. Thirty-three elderly patients with advanced NSCLC were enrolled in their phase II study of docetaxel 20 mg/m^2 and cisplatin 25 mg/m^2 on days 1, 8, and 15, doses which are similar to the recommended doses and schedule in our study. The overall response rate was 52%, the complete response rate was 6% and the median survival time was 12.4 months. Both response rate and median survival time in their study are promising and the results suggest that a docetaxel dose of 20 mg/m^2/week plus cisplatin dose of 25 mg/m^2/week has an antitumor effect as systemic chemotherapy.

The correlation with AAG was not a primary objective and this was not essential in this study. Thus, we could collect only 12 samples. The baseline AAG

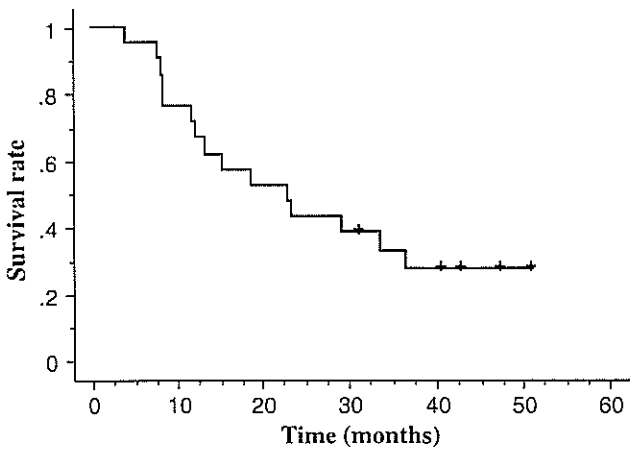

Fig. 2 Overall survival of patients treated with weekly docetaxel and cisplatin concomitant with TRT

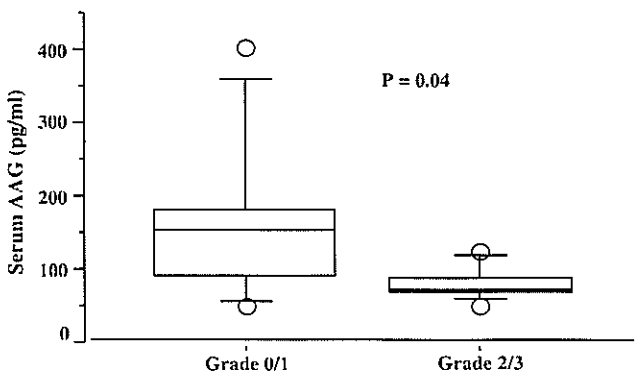

Fig. 3 Relationship between toxicity grade of esophagitis and serum AAG level

levels correlated significantly with the intensity of esophagitis in this study. The plasma AAG level was shown to be a significant predictor of pharmacodynamics in docetaxel treatment of NSCLC by Bruno et al. [20]. Since AAG strongly binds docetaxel, high AAG levels result in a lower free docetaxel fraction, and, therefore, decreased toxicity. The finding that high AAG decreased the grade of esophagitis was not unexpected.

In conclusion, the weekly combination of cisplatin and docetaxel concurrently with TRT is well tolerated and the recommended dose and schedule were determined to be cisplatin 25 mg/m^2 and docetaxel 20 mg/m^2 on days 1, 8, 15 of every 4 weeks, respectively. Because of favorable survival and acceptable toxicity profile, we consider this chemoradiotherapy as a warrant for further evaluation in phase II trials.

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ORIGINAL REPORT

Phase III Study of Docetaxel Compared With Vinorelbine in Elderly Patients With Advanced Non–Small-Cell Lung Cancer: Results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904)

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ABSTRACT

Purpose
Docetaxel has shown activity in elderly patients with advanced non–small-cell lung cancer (NSCLC). This randomized phase III trial evaluated the efficacy and safety of docetaxel versus vinorelbine (the current standard treatment) in elderly patients.

Patients and Methods
Chemotherapy-naïve patients age 70 years or older with stage IIIB/IV NSCLC and performance status 2 or lower were eligible. Patients randomly received docetaxel 60 mg/m^2 (day 1) or vinorelbine 25 mg/m^2 (days 1 and 8) every 21 days for four cycles. The primary end point was overall survival. Overall disease-related symptom improvement was assessed using an eight-item questionnaire.

Results
In total, 182 patients were enrolled. Median age was 76 years (range, 70 years to 86 years). There was no statistical difference in median overall survival with docetaxel versus vinorelbine (14.3 months *v* 9.9 months; hazard ratio, 0.780; 95% CI, 0.561 to 1.085; $P = .138$). There was a significant difference in median progression-free survival (5.5 months *v* 3.1 months; $P < .001$). Response rates were also significantly improved with docetaxel versus vinorelbine (22.7% *v* 9.9%; $P = .019$). The most common grade 3 to 4 toxicities were neutropenia (82.9% for docetaxel; 69.2% for vinorelbine; $P = .031$) and leukopenia (58.0% for docetaxel; 51.7% for vinorelbine). Other toxicities were mild and generally well tolerated. Docetaxel improved overall disease-related symptoms over vinorelbine (odds ratio, 1.86; 95% CI, 1.09 to 3.20).

Conclusion
Docetaxel improved progression-free survival, response rate, and disease-related symptoms versus vinorelbine. Overall survival was not statistically significantly improved at this time. Docetaxel monotherapy may be considered as an option in the standard treatment of elderly patients with advanced NSCLC.

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INTRODUCTION

Due to a general increase in life expectancy in developed countries worldwide, the proportion of the general population in these countries that is elderly is increasing. For example, in 1970 in Japan, 7.9% of the general population was 65 years or older, which increased to 17.3% by 2000, and is estimated to reach 29.6% by 2030.[1] As non–small-cell lung cancer (NSCLC) is a common disease in the elderly population, the question of how best to treat elderly NSCLC patients will become increasingly important.[2]

Chemotherapy in patients with advanced NSCLC improves survival, reduces disease-related symptoms, and improves quality of life (QOL) compared with best supportive care.[3] Although platinum-based doublets involving newer agents, such as docetaxel, paclitaxel, gemcitabine, vinorelbine, and irinotecan, are standard first-line chemotherapy for most patients with advanced NSCLC,[4,5] the use of these regimens in elderly patients remains a topic of debate.[2] The main reasons given for withholding standard platinum-based doublet regimens from elderly patients are age-related impairment of organ function, presence of potentially complicating

comorbid conditions, and a lower ability to tolerate the potential toxicity of combination chemotherapy than younger patients.

Three prospective randomized trials have investigated the optimal chemotherapy for elderly (70 years or older) NSCLC patients.[6-8] The Elderly Lung Cancer Vinorelbine Italian Study Group reported significantly superior survival and QOL with single-agent vinorelbine over best supportive care (median survival time, 6.4 months and 4.8 months, respectively; n = 161).[6] Two other studies have attempted to determine whether doublet regimens are optimal over single-agent therapy in elderly patients.[7,8] The conclusive results were reported in the Multicenter Italian Lung Cancer in the Elderly Study (MILES), which enrolled more than 700 patients and reported no significant survival difference between single-agent vinorelbine, single-agent gemcitabine, or a regimen with both agents combined.[8]

Docetaxel has demonstrated activity and acceptable toxicity in the treatment of advanced NSCLC, including elderly patients.[9-12] However, to date, no prospective randomized trials of docetaxel in elderly patients have been published. Two phase II trials of tri-weekly docetaxel 60 mg/m^2 (the recommended dose and schedule in Japan) have been performed in adult patients with NSCLC.[13,14] We conducted an exploratory, combined-subset analysis of the cohorts of patients age 70 years or older from these two trials: in 53 patients with a median age of 74 years (range, 70 years to 80 years), the median survival time was 10.3 months and the response rate was 24.5% (unpublished data). This encouraging retrospective result led us to design a prospective phase III trial to evaluate the efficacy of docetaxel versus vinorelbine in elderly patients with previously untreated advanced NSCLC, the results of which are reported herein.

PATIENTS AND METHODS

Eligibility Criteria

Chemotherapy- and radiotherapy-naïve patients with histologically or cytologically proven stage IIIB/IV NSCLC were enrolled. Other inclusion criteria included: age 70 years or older with a life expectancy of 3 months or longer; measurable and assessable disease; Eastern Cooperative Oncology Group performance status 2 or lower; adequate function of the bone marrow (leukocyte count, 4,000/μL or higher; absolute neutrophil count, 2,000/μL or higher; hemoglobin concentration, 9.5 g/dL or higher; platelet count, 100,000/μL or higher), kidney (serum creatinine, 1.2 mg/dL or lower), and liver (total bilirubin, 1.5× the institutional upper limits of normal or lower; AST and ALT 2.5× the institutional upper limits of normal or lower). Exclusion criteria included: presence of symptomatic brain metastasis or apparent dementia; active concomitant malignancy; massive pleural effusion or ascites; active infection; severe heart disease or grade 2 or higher ECG abnormality; uncontrolled diabetes mellitus, ileus, pulmonary fibrosis, diarrhea; bleeding tendency. All patients gave written informed consent and the protocol was approved by the institutional review board at each participating center.

Before treatment, all patients underwent a complete medical history and physical examination, chest radiography, fiberoptic bronchoscopy, chest and abdominal computed tomography (CT) scan, a brain CT or magnetic resonance imaging scan, an ECG, pulmonary function tests, and arterial blood gas analysis. A radionuclide bone scan was also performed to document the extent of the disease. Laboratory tests included a CBC with WBC differential, liver function tests, serum electrolytes, serum creatinine, blood urea nitrogen, and urinalysis.

The physical examination and laboratory tests were performed weekly. Chest radiography and/or CT were repeated every cycle to evaluate tumor response.

Treatment Plan

Patients were randomly assigned to receive a minimum of four cycles of tri-weekly docetaxel 60 mg/m^2 (1-hour intravenous infusion, day 1) or tri-weekly vinorelbine 25 mg/m^2 (intravenous infusion, days 1 and 8; weekly vinorelbine 25 mg/m^2 is the recommended dose in Japan[15]). Random assignment was centralized at the West Japan Thoracic Oncology Group (WJTOG) data center in Osaka, Japan; patients were stratified according to institution, disease stage (IIIB *v* IV), and performance status (0 to 1 *v* 2).

Vinorelbine was delayed on day 8 if leukocyte and platelet counts were lower than 2,000/μL and lower than 50,000/μL, respectively, and was withheld until the counts had recovered to 4,000/μL or higher and 100,000/μL or higher, respectively; patients were withdrawn from the study if longer than 5 weeks had elapsed from the time of the last treatment until these criteria were satisfied. The presence of grade 4 leukopenia and/or neutropenia led to reductions in the doses of docetaxel and vinorelbine by 10 mg/m^2 and 5 mg/m^2, respectively, in the subsequent cycle. Patients were withdrawn from the study in the event of progressive disease, consent withdrawal or grade 3 or higher nonhematologic toxicity without myelosuppression, nausea, vomiting, or alopecia. Second-line treatment was given at the physician's discretion.

Patients were evaluated for objective response before every cycle using WHO criteria.[16] A minimum duration of 4 weeks was required to document a response and the best response was recorded for each patient. Drug-induced toxicity was assessed before every cycle and was classified in accordance with National Cancer Institute Common Toxicity Criteria, version 2.0.[17] The worst data for each patient across all chemotherapy cycles were used in the toxicity analysis.

QOL Assessment

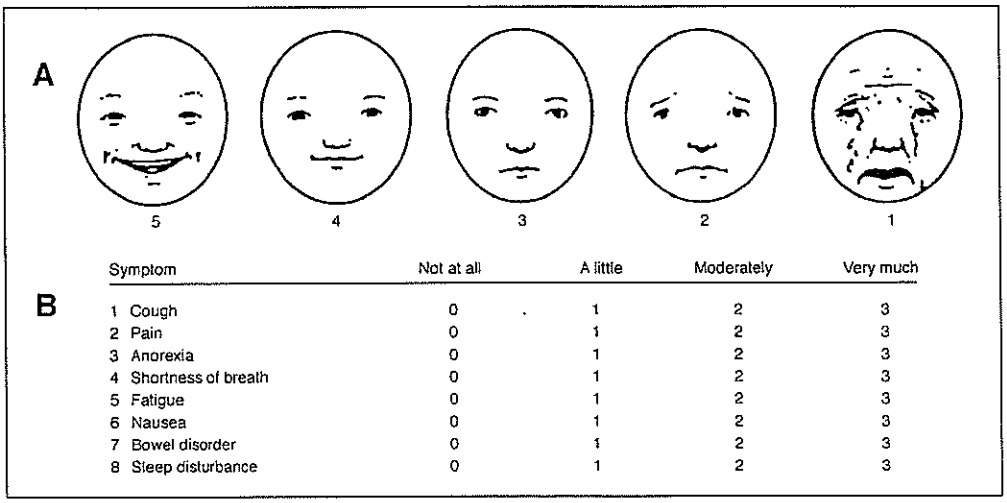
QOL was assessed using a self-administered questionnaire, which included a visual face scale for global QOL[18] (primary QOL analysis) and eight separate measures for assessing disease-related symptoms (secondary QOL analysis; Fig 1). The eight disease-related symptom items were derived from two sources: the disease-specific symptoms score for the first four items of the Lung Cancer Working Party, Medical Research Council[19] and the treatment-related symptoms for the last four items of the Functional Living Index, Cancer.[20] Patients completed the questionnaires at enrollment and at 3 weeks, 9 weeks, and 12 weeks. QOL was considered to have improved if the difference in score between any survey point and baseline was positive and to have worsened if the difference was negative.

Statistical Analysis

The primary objective was to determine whether docetaxel improved survival compared with vinorelbine. The study was designed with an 80% power using a two-sided log-rank test at a level of .05 to detect a 60% improvement in median survival time from 6.4 months with vinorelbine to 10.3 months with docetaxel; this required 90 patients per treatment arm. An interim analysis was performed after 120 patients were accrued; after the data had been reviewed, a decision was made to continue the study.

Survival analyses were conducted on the intent-to-treat population using follow-up data available at March 28, 2005. Overall survival was calculated from the start of therapy to the date of death from any cause or last follow-up. Progression-free survival was calculated from the start of therapy to the date of disease progression, recurrence, or death from any cause. Survival curves were estimated using the Kaplan-Meier method. A Cox proportional hazards regression model adjusted by the stratification factors (performance status, stage) was applied.

The χ^2 test was used in the response rate comparison and the toxicity analysis. For the QOL analyses, the comparison between the arms was conducted using generalized estimating equation regression models by GENMOD procedure in SAS (SAS Institute, Cary, NC).[21] An odds ratio of higher than 1 indicated that QOL was better with docetaxel than vinorelbine, achieving statistical significance if the 95% CI excluded 1.



B

Symptom	Not at all	A little	Moderately	Very much
1 Cough	0	1	2	3
2 Pain	0	1	2	3
3 Anorexia	0	1	2	3
4 Shortness of breath	0	1	2	3
5 Fatigue	0	1	2	3
6 Nausea	0	1	2	3
7 Bowel disorder	0	1	2	3
8 Sleep disturbance	0	1	2	3

Fig 1. (A) An illustration of the visual face scale for global quality of life and (B) the disease-related symptoms questionnaire.

RESULTS

Patient Characteristics

A total of 182 patients were enrolled and randomly assigned (90 to docetaxel, 92 to vinorelbine) between May 2000 and September 2003 from 32 institutions in WJTOG (Fig 2). Two patients were subsequently considered ineligible due to being entered twice in the study (n = 1, vinorelbine arm) and consent withdrawal immediately after random assignment (n = 1, docetaxel arm). Therefore, the intent-to-treat population comprised 180 patients: 89 assigned to docetaxel and 91 assigned to vinorelbine. One patient assigned to docetaxel developed disease progression before starting chemotherapy and was therefore not treated. Thus, toxicity and response were evaluated in 88 docetaxel patients and 91 vinorelbine patients.

Patients' baseline characteristics were well balanced between the treatment arms (Table 1). Although more patients receiving vinorelbine than docetaxel had a performance status of 2, the difference was not significant ($P = .057$).

The median number of treatment cycles was four in the docetaxel arm and three in the vinorelbine arm, which was significantly different ($P = .050$). Overall, 45 (51.1%) of 88 docetaxel patients and 37 (40.7%) of 91 vinorelbine patients completed four cycles of chemotherapy. The major reasons for treatment withdrawal in the docetaxel versus vinorelbine arms were disease progression (19.3% *v* 35.2%), adverse events (12.5% *v* 9.9%), physician's decision to withdraw patient (6.8% *v* 5.5%), protocol violation (3.4% *v* 3.3%), and consent withdrawal (2.3% *v* 3.3%). The relative dose intensities were 90.7% and 83.1% for docetaxel

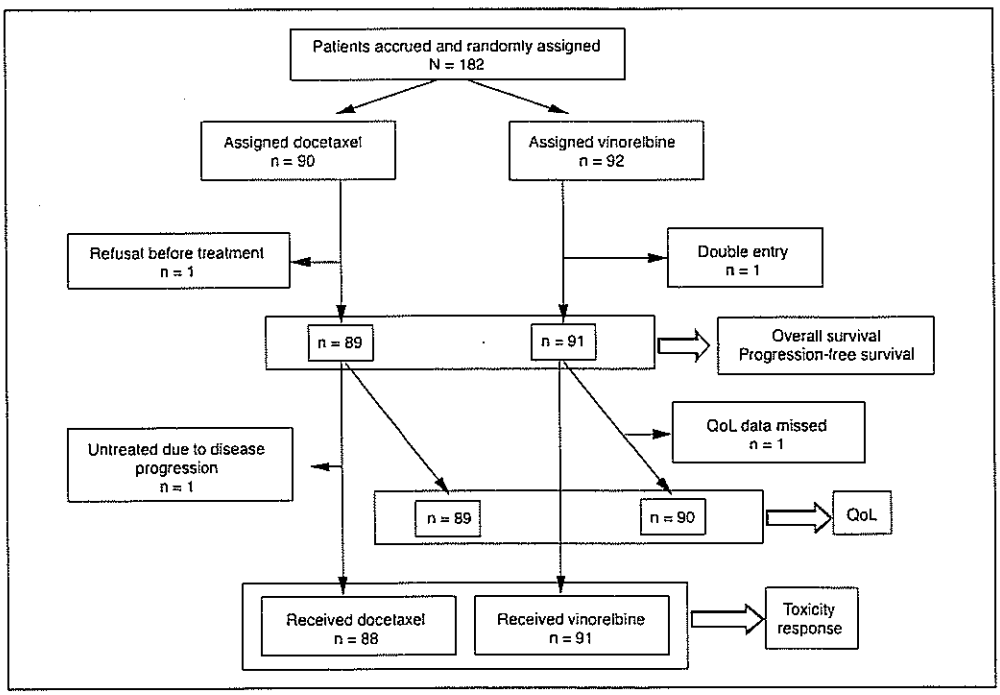


Fig 2. Flow diagram for the study. QoL, quality of life.

Table 1. Patient Characteristics

Characteristic	Docetaxel (n = 89) No. of Patients	%	Vinorelbine (n = 91) No. of Patients	%
Age, years				
Median	76		76	
Range	70-86		70-84	
Sex				
Male	69	77.5	68	74.7
Female	20	22.5	23	25.3
Performance status				
0-1	88	98.9	85	93.4
2	1	1.1	6	6.6
Stage				
IIIB	33	37.1	33	36.3
IV	56	62.9	58	63.7
Histology				
Adenocarcinoma	57	64.0	51	56.0
Squamous cell carcinoma	26	29.2	31	34.1
Other	6	6.7	9	9.9
Weight loss*				
> 10%	12	13.5	12	13.1
≤ 10%	77	86.5	78	85.7
Comorbid illness	38	42.6	36	39.6
None	51	57.3	55	60.4
Smoker	18	20.2	23	25.2
Never	71	79.8	68	74.7

*A data was not obtained from one vinorelbine patient.

and vinorelbine, respectively; most patients received the projected dose of chemotherapy in both treatment arms.

Second-line chemotherapy was administered to 85 patients (47.5%; 45 docetaxel patients and 40 vinorelbine patients). Among patients initially treated with docetaxel, five patients received second-line vinorelbine, while nine patients enrolled in the vinorelbine arm received crossover treatment with docetaxel. Fifty-two patients (29.0%) received second-line gefitinib: 33 patients (37.5%) in the docetaxel arm and 19 patients (20.9%) in the vinorelbine arm.

Response and Survival

Overall response rates significantly favored docetaxel over vinorelbine (22.7% *v* 9.9%; $P = .019$; Table 2). Progressive disease during treatment occurred in 37.4% of vinorelbine-treated patients and in 20.5% of docetaxel-treated patients; the difference between arms was significant ($P = .012$).

By March 28, 2005, 143 (79.4%) of 180 patients had died (docetaxel, 68; vinorelbine, 75). Median follow-up for survivors was 11.6 months. The median progression-free survival time with docetaxel was significantly longer than with vinorelbine (5.5 months *v* 3.1 months; hazard ratio, 0.606; 95% CI, 0.450 to 0.816; $P < .001$; Fig 3). Median survival time was 14.3 months and 9.9 months with docetaxel and vinorelbine, respectively. Although docetaxel prolonged median survival time by 4.4 months, the overall survival distributions were not statistically significant (hazard ratio, 0.780; 95% CI, 0.561 to 1.085; log-rank $P = .138$ and generalized Wilcoxon test $P = .065$; Fig 4). One-year survival rates were 58.6% and 36.7% for docetaxel and vinorelbine, respectively.

Toxicity

Overall, 179 patients were assessable for toxicity. Table 3 summarizes the major toxicities. Grade 3 to 4 neutropenia occurred in more patients in the docetaxel arm than in the vinorelbine arm ($P = .031$). However, there were no significant differences between the docetaxel and vinorelbine arms in the occurrence of grade 3 to 4 febrile neutropenia and infection. The incidence of grade 3 to 4 anemia was relatively low and there was no grade 2 or higher thrombocytopenia in either arm (Table 3). Alopecia (any grade) occurred significantly more frequently in the docetaxel arm than the vinorelbine arm ($P < .0001$). Overall toxicity in both treatment arms was generally mild and well tolerated in elderly patients with NSCLC.

One patient (age 76 years with stage IV disease and a performance status of 1) developed treatment-related interstitial pneumonia after three cycles of docetaxel; despite steroid pulse treatment, the patient died from this toxicity on day 65 after the start of the third treatment cycle.

QOL

Baseline QOL data were available for all patients except one vinorelbine patient (for whom data were not collected due to human error; Fig 2). Thus, 179 patients completed baseline questionnaires; questionnaire completion rates were 92.2% at 3 weeks, 83.2% at 9 weeks, and 69.8% at 12 weeks. Compliance rates were not significantly different between the arms ($P = .311$). QOL data were missing in 28 surveys due to death or severe impairment of the patient's general condition; this accounted for 3.9% of the total number of surveys scheduled. The proportions of data missing at baseline and at 3 weeks, 9 weeks, and 12 weeks were 0%, 1.1%, 2.3%, and 6.7% in the docetaxel

Table 2. Response to Treatment

Response	Docetaxel (n = 88) No. of Patients	%	Vinorelbine (n = 91) No. of Patients	%
Complete response	0		0	
Partial response	20	22.7	9	9.9
Stable disease	47	53.4	45	49.5
Progressive disease	18	20.5	34	37.4
Not assessable	3	3.4	3	3.3
Overall response rate	22.7		9.9	
95% CI	13.9 to 31.5		3.8 to 16.0	

NOTE. $P = .019$.

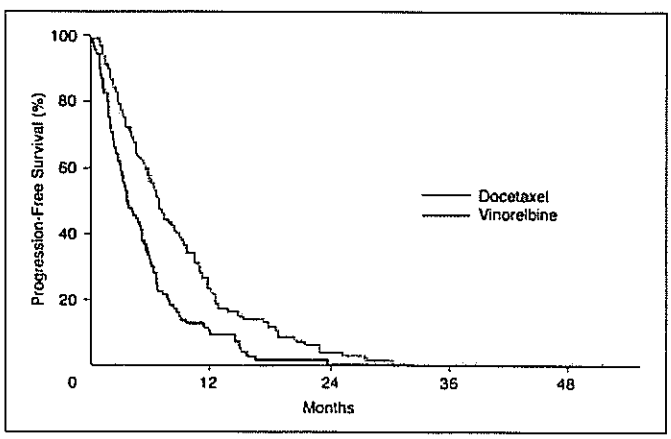


Fig 3. Progression-free survival curves for patients treated with docetaxel (n = 89) or vinorelbine (n = 91).

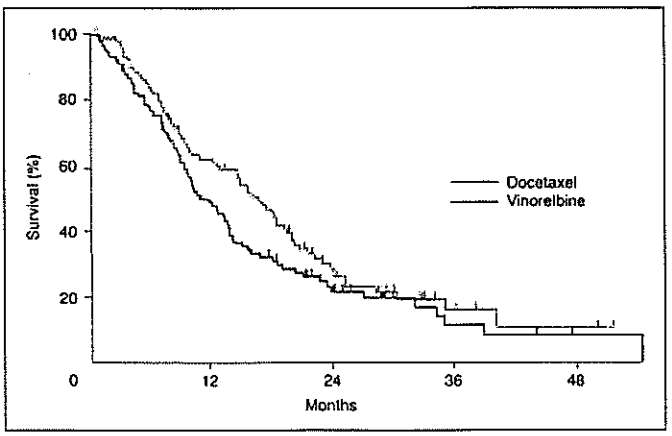


Fig 4. Overall survival curves for patients treated with docetaxel (n = 89) or vinorelbine (n = 91).

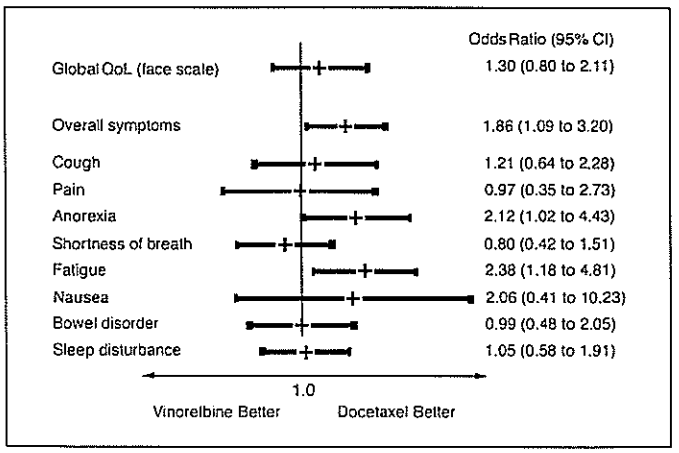


Fig 5. Forest plot of odds ratio for global quality of life (QoL) and disease-related symptoms analyses.

arm compared with 0%, 1.1%, 6.6%, and 13.2% in the vinorelbine arm. The distribution of the missing data was not significantly different between the treatment arms ($P = .150$). In terms of global QOL, no significant difference was observed between the two arms (odds ratio, 1.30; 95% CI, 0.80 to 2.11; Fig 5). Docetaxel was associated with significantly better improvement in the overall symptom score than vinorelbine (odds ratio, 1.86; 95% CI, 1.09 to 3.20; Fig 5). When the eight-symptom scores were analyzed separately, the docetaxel arm showed significantly better improvement in anorexia and fatigue than the vinorelbine arm. These results did not change when the QOL data were reanalyzed with the missing information from the 28 surveys assigned as unimproved.

DISCUSSION

This phase III trial showed that docetaxel provided significantly longer progression-free survival (5.5 months *v* 3.1 months; $P < .001$), a significantly higher overall response rate (22.7% *v* 9.9%; $P = .019$), a more favorable 1-year survival rate (58.6% *v* 36.7%) and significantly better disease-related symptom improvement than vinorelbine in elderly patients with advanced NSCLC. However, although docetaxel-treated patients also experienced a longer median survival time (14.3 months *v* 9.9 months) than vinorelbine-treated patients, the primary end point of improved overall survival with docetaxel was not achieved. Possible reasons for failing to detect a significant difference between the docetaxel and vinorelbine survival curves may include an

Table 3. Toxicities

Toxicity	Docetaxel (n = 88) Grade (%)				Vinorelbine (n = 91) Grade (%)			
	1	2	3	4	1	2	3	4
Leukopenia	10.2	27.3	52.3	5.7	6.6	30.8	35.2	16.5
Neutropenia	0	6.8	26.1*	56.8*	2.2	9.9	30.8*	38.5*
Anemia (Hb)	59.1	36.4	2.3	1.1	41.8	42.9	8.8	1.1
Thrombocytopenia	13.6	0	0	0	26.4	0	0	0
AST	22.7	2.3	1.1	0	24.2	4.4	3.3	0
ALT	27.3	3.4	1.1	0	19.8	5.5	2.2	0
Creatinine	11.4	0	0	1.1	9.9	0	0	3.3
Nausea	25.0	17.0	10.2	0	20.9	14.3	8.8	0
Vomiting†	9.1	3.4	0	0	0	1.1	1.1	0
Febrile neutropenia	—	—	12.5	0	—	—	11.0	0
Infection	4.5	15.9	11.4	0	5.5	7.7	13.2	0
Constipation	26.1	14.8	2.3	0	18.7	20.9	5.5	1.1
Diarrhea	15.9	5.7	4.5	0	14.3	3.3	1.1	0
Mucositis‡	10.2	5.7	0	0	3.3	0	0	0
Alopecia§	45.5	28.4	—	—	30.8	0	—	—
Peripheral neuropathy	12.5	1.1	0	0	7.7	0	0	0

NOTE. *P* values ware obtained by χ^2 test.
Abbreviation: Hb, hemoglobin.
*Indicates grade 3 to 4 neutropenia; $P = .031$.
†Indicates grade 1 to 4 vomiting; $P = .007$.
‡Indicates grade 1 to 4 mucositis; $P = .004$.
§Indicates grade 1 to 2 alopecia; $P < .001$.

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 (47.5%) subsequently receiving second-line therapy. Another reason may have been the small sample size and the prespecified aim of detecting an improvement in survival from 6.4 months to 10.3 months. The selection of a median survival in the reference arm of 6.4 months for the sample size calculation was based on the results of the Elderly Lung Cancer Vinorelbine Italian Study Group study.[6] However, more recent survival data from the MILES study[8] reporting a median survival of 8.3 months with vinorelbine may have been more appropriate. Had this value been used in the sample size calculation a larger study population would have been required which would likely have allowed the present analysis to detect statistically significant differences between the treatment arms.

The survival findings with vinorelbine in this study were similar to or slightly better than those reported in other studies; vinorelbine monotherapy in elderly NSCLC patients has previously shown median survival times of 4.5 months to 8.3 months and 1-year survival rates of 13% to 38%.[6-8] One reason for a slightly longer median survival time in our study may be the relatively better prognosis of the enrolled patients. Interestingly, the median survival time of 14.3 months with docetaxel in this study appears to be similar to that reported for platinum-doublet chemotherapies assessed in a recent Japanese randomized trial in chemotherapy-naïve NSCLC patients, which reported median survival times of 11.4 months to 14.8 months.[5] The improved overall survival time in the docetaxel arm may be attributed to gefitinib treatment as a second-line treatment. Japanese patients are sensitive to gefitinib, and 37% of patients who were treated with docetaxel also received gefitinib, compared with 20.9% of vinorelbine treated patients although this difference may be attributable to the numerically greater number of patients alive after initial docetaxel treatment. Crossover to second-line chemotherapy was permitted in this protocol and could have also influenced outcomes. However, as only a small number of patients in either treatment arm were treated with alternative chemotherapy as salvage (five patients from the docetaxel arm and nine patients from the vinorelbine arm), outcomes for these patients were not felt to significantly alter the overall results of the study.

Age should still be taken into consideration when selecting appropriate chemotherapy in the clinical setting given the likelihood of metabolic changes with advancing age, the increased likelihood of comorbidities, and general lack of clinical trial data specifically in older patients.

The toxicity profiles for both treatment arms were generally mild and tolerable in this study. Although severe neutropenia occurred significantly more often with docetaxel, there were no differences in the incidence of febrile neutropenia or other hematologic toxicities between the two arms. The incidence of grade 3 to 4 neutropenia (69.3%) with vinorelbine treatment in our study was somewhat higher than that reported in the MILES (25%).[8] The reason for these differences is unclear. In our study, patients treated with docetaxel experienced a relatively higher incidence of severe neutropenia compared with patients treated with vinorelbine, although the incidence with docetaxel was similar to that seen in Japanese phase II studies of docetaxel in patients with advanced NSCLC (87%, grade 3-4 neutropenia).[13] However, the incidences of grade 3 febrile neutropenia and grade 3 infection were relatively low and similar between the treatment arms in our study. Importantly, there was no difference in global QOL between the treatment arms. Furthermore, docetaxel significantly improved QOL in terms of disease-related symptoms compared with vinorelbine.

The WJTOG 9904 study is the first prospective, randomized, phase III trial of taxane monotherapy for elderly patients with advanced NSCLC, and has shown encouraging efficacy with single-agent docetaxel. To further improve outcomes, we would suggest that the next step for treating elderly patients might be to prospectively investigate platinum-doublet regimens, particularly docetaxel with carboplatin, in phase III trials. Retrospective analyses suggest that platinum doublets are effective and tolerable in fit, elderly patients.[2,22-24] For further future studies in elderly patients, it would be of interest to investigate regimens involving docetaxel combined with a molecular-targeted agent (such as gefitinib, erlotinib,[25] or bevacizumab), as molecular-targeted agents are associated with relatively mild toxicity profiles compared with cytotoxic agents.

In conclusion, docetaxel improved response rate, progression-free survival, and overall disease-related symptoms compared with vinorelbine in elderly patients with advanced NSCLC; overall survival was not significantly improved. Based on these results, docetaxel monotherapy may be considered as an option in the standard treatment of elderly patients with advanced NSCLC.

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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

The authors indicated no potential conflicts of interest.

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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 ≥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 ≥3500/μL, neutrophil count ≥2000/μL, hemoglobin concentration ≥10.0 g/dL, platelet count ≥ 100,000/μL), kidney function (creatinine ≤1.2 mg/dL), liver function (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels ≤2.5 times the upper limit of normal; and total bilirubin ≤1.5 mg/dL), and pulmonary function (partial pressure of alveolar oxygen ≥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 × (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 ≥1, constipation Grade ≥3, and/or other nonhematologic toxicities Grade ≥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

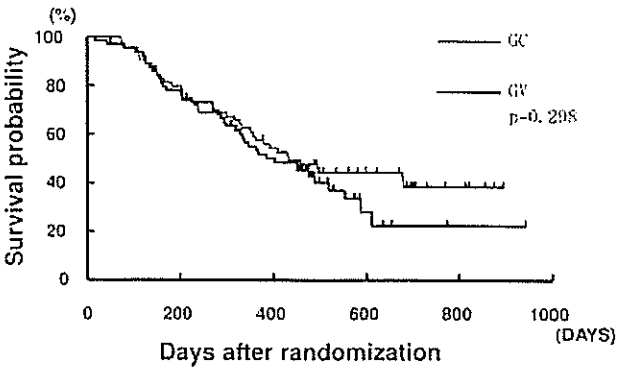

FIGURE 1. Overall survival is illustrated for the 2 treatment arms. GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.

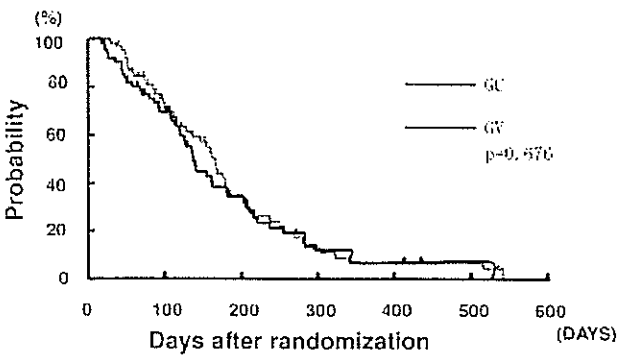

FIGURE 2. Progression-free survival is illustrated for the 2 treatment arms. GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.

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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