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
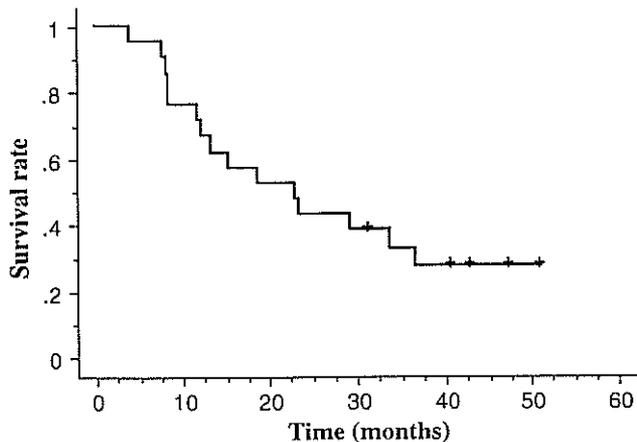
Fig. 2 Overall survival of patients treated with weekly docetaxel and cisplatin concomitant with TRT
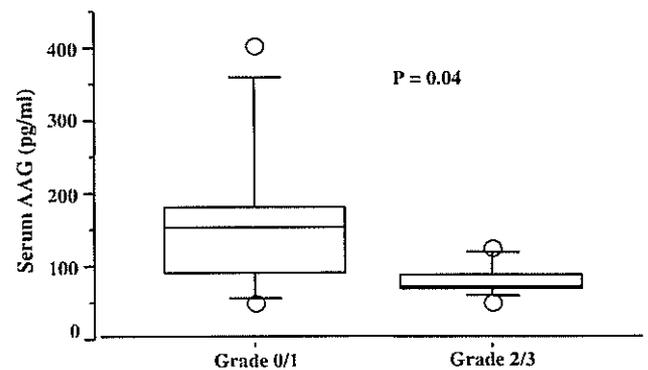
Fig. 3 Relationship between toxicity grade of esophagitis and serum AAG level

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.

References

1. Dillman RO, Herndon J, Seagren SL et al (1996) Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst 88:1210–1215
2. Le Chevalier T, Arriagada R, Quiox E et al (1991) Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of randomized trial in 353 patients. J Natl Cancer Inst 83:417–423
3. Sause W, Kolesar P, Taylor S et al (2000) Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer. Chest 117:358–364
4. Schaake-Koning C, van den Bogaert W, Dalesio M et al (1992) Effects of concurrent cisplatin and radiotherapy on inoperable non-small-cell lung cancer. N Engl J Med 326:524–530
5. Jeremic B, Shibamoto Y, Acimovic L et al (1996) Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small-cell lung cancer: a randomized study. J Clin Oncol 14:1065–1070
6. Non-small Cell Lung Cancer Collaborative Group (1995) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Br Med J 311:899–909
7. Furuse K, Fukuoka M, Kawahara M et al (1999) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung caner. J Clin Oncol 17:2692–2699
8. Curran WJ Jr, Scott C, Langer C et al (2000) Phase III comparison of sequential vs concurrent chemoradiation for PTS with unresected stage III non-small cell lung cancer (NSCLC): Initial report of Radiation Therapy Oncology Group (RTOG) 9410. Proc Am Soc Clin Oncol 19:484a
9. Hei TK, Piao CQ, Geard CR et al (1994) Taxol and ionizing radiation: interaction and mechanisms. Int J Radiat Oncol Biol Pys 29(2):267–271
10. Hennequim C, Giocanti N, Favaudon V (1996) Interaction of ionizing radiation with paclitaxel (Taxol) and docetaxel (Taxotere) in HeLa and SQ20B cells. Cancer Res 56(8):1842–1850
11. Choy H, Rodriguez F, Koester S et al (1992) Synergistic effects of toxol/taxotere on radiation sensitivity on human cell lines. Int J Radiat Oncol Biol Phys 24(suppl):274–275
12. Mauer AM, Masters GA, Haraf DJ et al (1998) Phase I study of docetaxel with concomitant thoracic radiation therapy. J Clin Oncol 16:159–164
13. Aamdal S, Wibe E, Hallen MN et al (1997) Phase I study of concomitant docetaxel (Taxotere) and radiation in locally advanced non-small-cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 16:460a
14. Koukourakis MI, Kourousis C, Kamilaki M et al (1998) Weekly docetaxel and concomitant boost radiotherapy for non-small cell lung cancer. A phase I/II dose escalation trial. Eur J Cancer 34:838–844
15. Koukourakis MI, Giatromanolaki A, Schiza S et al (1999) Concurrent twice-a-week docetaxel and radiotherapy: a dose escalation trial with immunological toxicity evaluation. Int J Radiat Oncol Biol Phys 43:107–113
16. Aamdal S, Hagen I, Avril I et al (1999) Docetaxel (D, Taxotere) with concurrent radiation in locally advanced non-small cell lung cancer. Proc Am Clin Oncol 18:479a
17. Koukourakis MI, Bahlitzanakis N, Froudarakis M et al (1999) Concurrent conventionally fractionated radiotherapy and weekly docetaxel in the treatment of stage IIIb non-small-cell lung carcinoma. Br J Cancer 80:1792–1796
18. Dewitt L (1987) Combined treatment of radiation and cisdiamminedichloroplatinum (II): a review of experimental and clinical data. Int J Radiat Oncol Biol Phys 13:403–426
19. Urien S, Barre J, Morin C et al (1996) Docetaxel serum protein binding with high affinity to alpha1-acid gylcoprotein. Invest New Drug 14:147–151
20. Bruno R, Hille D, Riva A et al (1998) Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol 16:187–196
21. Robert F, Spencer SA, Childs HA III et al (2002) Concurrent chemoradiation therapy with cisplatin and paclitaxel for locally advanced non-small cell lung cancer: long-term follow-up of a phase I study. Lung Cancer 37(2):189–199
22. Kiura K, Ueoka H, Segawa Y et al (2003) Phase I/II study of docetaxel and cisplatin with concurrent thoracic radiation therapy for locally advanced non-small-cell lung cancer. Br J Cancer 89:795–802
23. Wu HG, Bang YJ, Choi EK et al (2002) Phase I study of weekly docetaxel and cisplatin concurrent with thoracic radiotherapy in stage III non-small-cell lung cancer. Int J Rad Oncol Biol Phys 52(1):75–80
24. Werner-Wasik M, Pequignot E, Leeper D et al (2000) Predictors of severe esophagitis include use of concurrent chemotherapy, but not the length of irradiated esophagus: a multivariate analysis of patients with lung cancer treated with nonoperative therapy. Int J Radiat Oncol Biol Phys 48(3):689–696
25. Tsujino K, Hirota S, Endo M et al (2003) Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 55(1):110–115
26. Singh AK, Lockett MA, Bradley JD (2003) Predictors of radiation-induced esophageal toxicity in patients with non-small-cell lung cancer treated with three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 55(2):337–341
27. Niho S, Ohe Y, Yokoyama A et al (2003) A phase II study of docetaxel (D) and cisplatin (C) (DC) administered as three consecutive weekly infusions in elderly patients (pts) with advanced non-small cell lung cancer. Proc Am Soc Clin Oncol 22:679

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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

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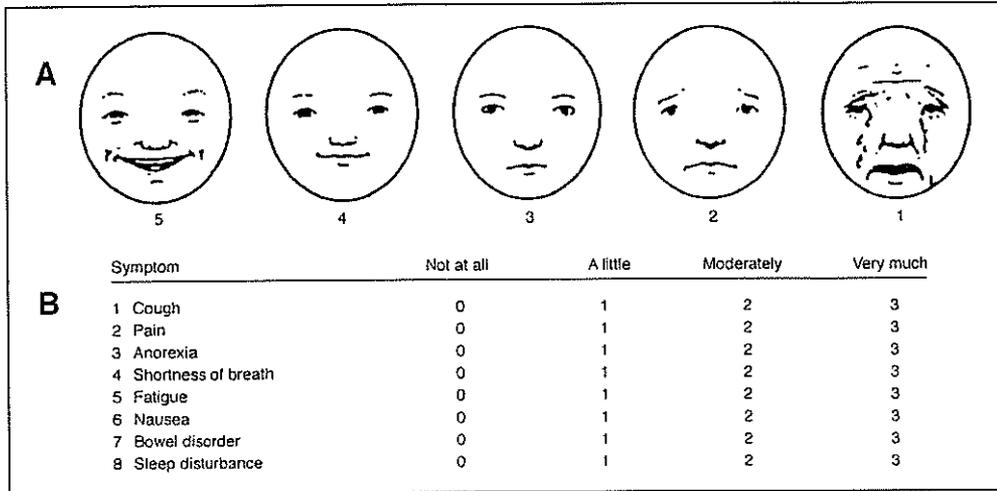
Fig 1. (A) An illustration of the visual face scale for global quality of life and (B) the disease-related symptoms questionnaire.

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

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
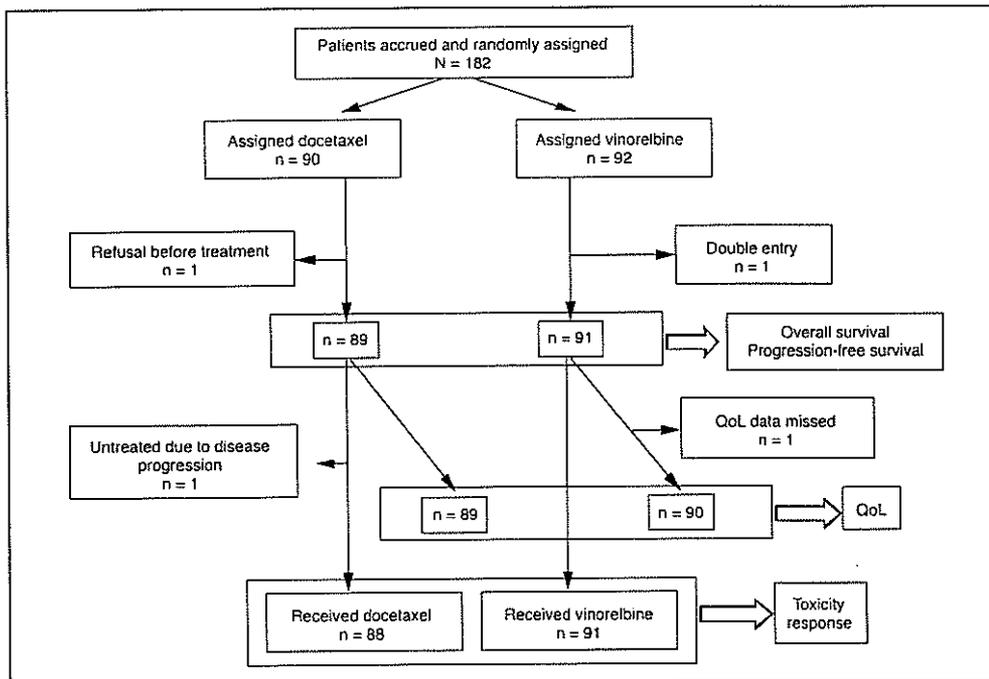

Fig 2. Flow diagram for the study. QoL, quality of life.

Table 1. Patient Characteristics

Characteristic	Docetaxel (n = 89)		Vinorelbine (n = 91)	
	No. of Patients	%	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

Table 2. Response to Treatment

Response	Docetaxel (n = 88)		Vinorelbine (n = 91)	
	No. of Patients	%	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.

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
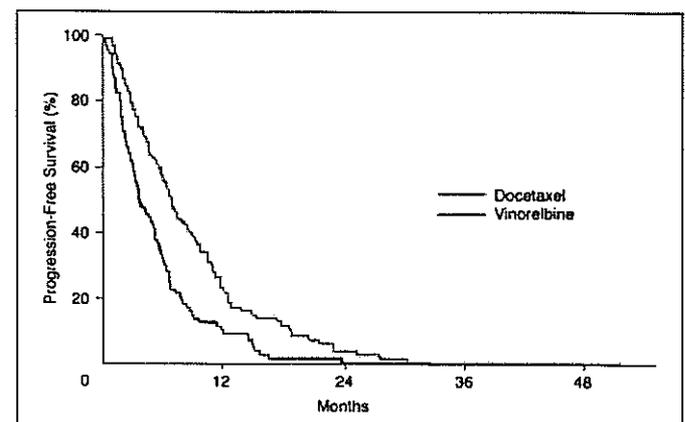

Fig 3. Progression-free survival curves for patients treated with docetaxel (n = 89) or vinorelbine (n = 91).
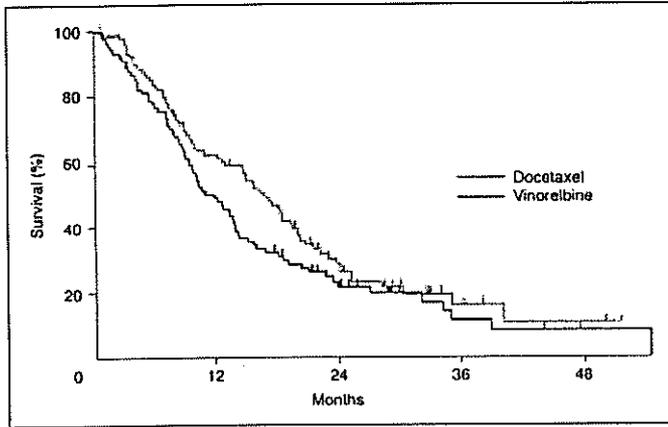
Fig 4. Overall survival curves for patients treated with docetaxel (n = 89) or vinorelbine (n = 91).

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.
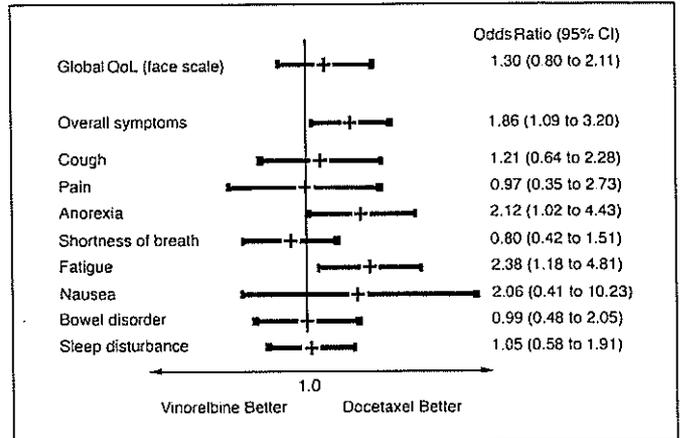
DISCUSSION

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

Toxicity	Docetaxel (n = 88)				Vinorelbine (n = 91)			
	Grade (%)				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

Table 3. Toxicities

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.

REFERENCES

1. National Institute of Population and Social Security Research: Population Projections for Japan: 2001-2050, 2005. http://www.ipss.go.jp

2. Gridelli C, Shepherd FA: Chemotherapy for elderly patients with non-small cell lung cancer: A review of the evidence. Chest 128:947-957, 2005

3. Non-Small Cell Lung Cancer Co-operative Group: Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomized clinical trials. BMJ 311:899-909, 1995

4. Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92-98, 2002

5. Kubota K, Nishiwaki Y, Ohashi Y, et al: The Four-Arm Cooperative Study (FACS) for advanced non-small-cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 22:14S, 2004 (abstr 7006)

6. The Elderly Lung Cancer Vinorelbine Italian Study Group: Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 91:66-72, 1999

7. Frasci G, Lorusso V, Panza N, et al: Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol 18:2529-2536, 2000

8. Gridelli C, Perrone F, Gallo C, et al: Chemotherapy for elderly patients with advanced non-small-cell lung cancer: The Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 95:362-372, 2003

9. Takigawa N, Segawa Y, Kishino D, et al: Clinical and pharmacokinetic study of docetaxel in elderly non-small-cell lung cancer patients. Cancer Chemother Pharmacol 54:230-236, 2004

10. Ohe Y, Niho S, Kakinuma R, et al: A phase II study of cisplatin and docetaxel administered as three consecutive weekly infusions for advanced non-small-cell lung cancer in elderly patients. Ann Oncol 15:45-50, 2004

11. Yoshimura N, Kudoh S, Negoro S, et al: A phase II study of docetaxel in elderly patients with advanced non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 19:532a, 2000 (abstr 2093)

12. Hainsworth JD, Burris HA 3rd, Litchy S, et al: Weekly docetaxel in the treatment of elderly patients with advanced nonsmall cell lung carcinoma: A Minnie Pearl Cancer Res Network Phase II Trial. Cancer 89:328-333, 2000

13. Kunitoh H, Watanabe K, Onoshi T, et al: Phase II trial of docetaxel in previously untreated advanced non-small-cell lung cancer: A Japanese cooperative study. J Clin Oncol 14:1649-1655, 1996

14. Kudo S, Hino M, Fujita A, et al: Late phase II clinical study of RP56976 (docetaxel) in patients with non-small cell lung cancer. Gan To Kagaku Ryoho21:2617-2623, 1994 (Japanese)

15. Furuse K, Kubota K, Kawahara M, et al: A phase II study of vinorelbine, a new derivative of vinca alkaloid, for previously untreated advanced non-small cell lung cancer: Japan Vinorelbine Lung Cancer Study Group. Lung Cancer 11:385-391, 1994

16. Miller AB, Hoogstraten B, Staquet M, et al: Reporting results of cancer treatment. Cancer 47: 207-214, 1981

17. National Cancer Institute: Common Toxicity Criteria, version 2. Bethesda, MD, Division of Cancer Treatment and Diagnosis, National Cancer Institute, 1999 http://www.fda.gov/cder/cancer/toxicityframe.htm

18. Kurihara M, Shimizu H, Tsuboi K, et al: Development of quality of life questionnaire in Japan: Quality of life assessment of cancer patients receiving chemotherapy. Psychol Oncol 8:355-363, 1999

19. Stephens RJ, Hopwood P, Girling DJ: Defining and analysing symptom palliation in cancer clinical trials: A deceptively difficult exercise. Br J Cancer 79:538-544, 1999

20. Schipper H, Clinch J, McMurray A, et al: Measuring the quality of life of cancer patients: The Functional Living Index – Cancer: Development and validation. J Clin Oncol 2:472-483, 1984

21. Kianifard F, Gallo PP: Poisson regression analysis in clinical research. J Biopharm Stat 5:115-129, 1995

22. Langer CJ, Manola J, Bernardo P, et al: Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: Implications of Eastern Cooperative Oncology Group 5592, a randomized trial. J Natl Cancer Inst 94:173-181, 2002

23. Belani CP, Fossella F.: Elderly subgroup analysis of a randomized phase III study of docetaxel

plus platinum combinations versus vinorelbine plus cisplatin for first-line treatment of advanced non small cell lung carcinoma (TAX 326).Cancer 104: 2766-2774, 2005

24. Fossella F, Pereira JR, von Pawel J, et al: Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: The TAX 326 study group. J Clin Oncol 21:3016-3024, 2003

25. Davies AM, Lara PN, Lau DH, et al: Intermittent erlotinib in combination with docetaxel (DOC): Phase I schedules designed to achieve pharmacodynamic separation. Proc Am Soc Clin Oncol 23: 630s, 2005 (abstr 7038)

Acknowledgment

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.

U nfortunately, 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]

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 $\geq 3500/\mu L$, neutrophil count $\geq 2000/\mu L$, hemoglobin concentration ≥ 10.0 g/dL, platelet count $\geq 100,000/\mu L$), 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/m² 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/m² in 100 mL of normal saline solution as a 30-minute intravenous infusion and vinorelbine 25 mg/m² 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 $<2000/\mu L$, platelet count $<75,000/\mu L$, 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 $\geq 3000/\mu L$, neutrophil count $\geq 1500/\mu L$, platelet count $\geq 100,000/\mu L$, creatinine ≤ 1.5 mg/dL, AST and ALT levels ≤ 2.5 times the upper limit of normal, and total bilirubin ≤ 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 $(< 20,000/\mu L)$, nonhemotologic toxicity Grade ≥ 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 ≥ 3 anemia and in patients who had platelet counts $\leq 20,000/\mu L$ 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 ≥ 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 ≥ 1 nontarget lesion(s). PD was defined as the appearance of ≥ 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

TABLE 2
Treatment Delivery and Dose Reduction Rate

No. of cycles	Gemcitabine and carboplatin		Gemcitabine and vinorelbine	
	No. of patients (%)	No. of patients who required dose reduction (%)	No. of patients (%)	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

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.

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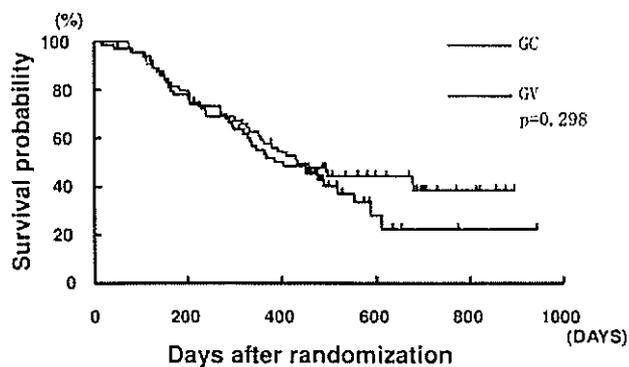
FIGURE 1. Overall survival is illustrated for the 2 treatment arms. GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.
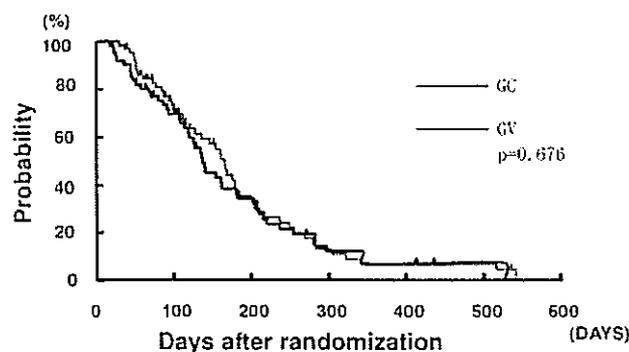

FIGURE 2. Progression-free survival is illustrated for the 2 treatment arms. GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.

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

Toxicity	No. of patients (%)		P
	GC	GV	
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).

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 non-

hematologic 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.

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 amino-transferase; 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.

REFERENCES

1. Non-Small Cell Lung Cancer Collaborative Groups. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. *BMJ.* 1995;311:899–909.
2. Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol.* 2004; 22:330–353.
3. D'Addario G, Pintilie M, Leighl NB, et al. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. *J Clin Oncol.* 2005;23:2926–2936.
4. Paccagnella A, Favaretto A, Oniga F, et al. Cisplatin versus carboplatin in combination with mitomycin and vinblastine in advanced non small cell lung cancer. A multicenter, randomized Phase III trial. *Lung Cancer.* 2004;43:83–91.
5. Rosell R, Gatzemeier U, Betticher DC, et al. Phase III randomised trial comparing paclitaxel/carboplatin with paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: a cooperative multinational trial. *Ann Oncol.* 2002;13: 1539–1549.
6. Mazzanti P, Massacesi C, Rocchi MB, et al. Randomized, multicenter, Phase II study of gemcitabine plus cisplatin versus gemcitabine plus carboplatin in patients with advanced non-small cell lung cancer. *Lung Cancer.* 2003;41:81–89.
7. Zatloukal P, Petruzelka L, Zemanova M, et al. Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in Stage IIIb and IV non-small cell lung cancer: a Phase III randomized trial. *Lung Cancer.* 2003;41:321–331.
8. Sederholm C, Hillerdal G, Lamberg K, et al. Phase III trial of gemcitabine plus carboplatin versus single-agent gemcitabine in the treatment of locally advanced or metastatic non-small-cell lung cancer: the Swedish Lung Cancer Study Group. *J Clin Oncol.* 2005;23:8380–8388.
9. Katakami N, Sugiura T, Nogami T, et al. Combination chemotherapy of gemcitabine and vinorelbine for patients in Stage IIIB-IV non-small cell lung cancer: a Phase II study of the West Japan Thoracic Oncology Group (WJTOG) 9908. *Lung Cancer.* 2004;43:93–100
10. Gridelli C, Gallo C, Shepherd FA, et al. Gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small-cell lung cancer: a Phase III trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2003;21:3025–3034.
11. Laack E, Dickgreber N, Muller T, et al. Randomized Phase III study of gemcitabine and vinorelbine versus gemcitabine, vinorelbine, and cisplatin in the treatment of advanced non-small-cell lung cancer: from the German and Swiss Lung Cancer Study Group. *J Clin Oncol.* 2004;22:2348–2356.
12. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol.* 1989;7:1748–1756.
13. Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine. *Nephron.* 1992;62:249–256.
14. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92:205–216.
15. Rudd RM, Gower NH, Spiro SG, et al. Gemcitabine plus carboplatin versus mitomycin, ifosfamide, and cisplatin in patients with Stage IIIB or IV non-small-cell lung cancer: a Phase III randomized study of the London Lung Cancer Group. *J Clin Oncol.* 2005;23:142–153.
16. Alberola V, Camps C, Provencio M, et al. Cisplatin plus gemcitabine versus a cisplatin-based triplet versus nonplatinum sequential doublets in advanced non-small-cell lung cancer: a Spanish Lung Cancer Group Phase III randomized trial. *J Clin Oncol.* 2003;21:3207–3213.
17. Gandara DR, Ohe Y, Kubota K, et al. Japan-SWOG common arm analysis of paclitaxel/carboplatin in advanced stage non-small cell lung cancer (NSCLC): a model for prospective comparison of cooperative group trials. *Proc Am Soc Clin Oncol.* 2004;23:616. Abstract 7007.

A Phase II Study of the Global Dose and Schedule of Capecitabine in Japanese Patients with Metastatic Colorectal Cancer

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Background: Although the standard 3-week capecitabine regimen (1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest) has shown superior activity and improved safety over bolus 5-fluorouracil/leucovorin in two large randomized phase III trials in Europe and in the United States, only a 4-week regimen of capecitabine (828 mg/m^2 twice daily for 3 weeks) has been studied in Japan. Therefore, we performed a phase II study to investigate the 3-week regimen of capecitabine in Japanese patients with metastatic colorectal cancer (MCRC).

Methods: Previously untreated patients with MCRC received oral capecitabine 1250 mg/m^2 twice daily for 2 weeks. Treatment was repeated every 3 weeks. Blood and urine samples were collected for pharmacokinetic analysis.

Results: Sixty patients were enrolled. The overall response rate was 35% [95% confidence interval (CI), 23–48%], and 52% of patients had stable disease. The median time to progression was 5.5 months (95% CI, 4.2–6.7 months). The median overall survival was 20.2 months (95% CI, 16.6–27.8 months). The most frequently occurring adverse drug reaction was hand-foot syndrome (all-grade 73%; grade 3 13%). Diarrhea, anorexia, nausea and stomatitis were each seen in 37% of patients. The pharmacokinetic profiles of capecitabine and its metabolites were similar to those reported in Caucasian patients.

Conclusions: The 3-week regimen of capecitabine was effective and well tolerated in Japanese patients with MCRC as well, and could be used as the basic regimen for future combination therapies.

Key words: capecitabine – colorectal cancer – phase II study

INTRODUCTION

For more than 40 years, 5-fluorouracil (5-FU) has been the mainstay of treatment for patients with metastatic colorectal cancer (MCRC). Many incremental improvements to 5-FU regimens, such as biomodulation with leucovorin (LV) and schedule modification, have been made. For example, infusional 5-FU offers not only improved response rates, but also a small survival benefit, compared with those of bolus 5-FU according to data from randomized trials and meta-analyses (1,2). However, continuous infusions require venous access lines and pumps with significant associated costs. Consequently, patients prefer to receive oral rather than intravenous chemotherapy (3,4).

Several new fluoropyrimidines, including uracil plus tegafur (UFT), capecitabine and S-1, have been developed and evaluated in the treatment of colorectal cancer. Capecitabine (Xeloda®) is an oral fluoropyrimidine carbamate designed in Japan to deliver 5-FU predominantly to tumor cells. After oral administration, capecitabine is rapidly and extensively absorbed through the intestine as an intact molecule, and then metabolized to 5-FU in three steps. In the first step, capecitabine is hydrolyzed to 5′-deoxy-5-fluorocytidine (5′-DFCR) by carboxylesterase primarily in the liver. 5′-DFCR is then converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by cytidine deaminase, which is highly active in

tumor cells and in the liver. Thymidine phosphorylase, which is significantly more active in tumor tissues than in adjacent normal tissues, finally converts 5′-DFUR to 5-FU (5,6). With each successive conversion step, the potential for systemic exposure to 5-FU is reduced while 5-FU delivery to tumor tissues is increased. Consequently, capecitabine avoids many of the gastrointestinal toxicities commonly observed with 5-FU.

Many clinical studies of capecitabine in MCRC have been conducted worldwide. In a Japanese phase I study using continuous administration of capecitabine, the maximum tolerated dose was 1255 mg/m^2 twice daily; skin fissures and gastric ulcers were noted as the dose-limiting toxicities (7). Another phase I study showed that a 1-week rest period appealed to patients and also maintained the activity of capecitabine therapy (8). From these findings, a 4-week intermittent regimen (3 weeks of capecitabine 828 mg/m^2 twice daily followed by a 1-week rest period) was recommended for Japanese phase II studies. This 4-week intermittent schedule of capecitabine was active and well tolerated in Japan, resulting in response rates of 25% (5/20) in a small pilot study (9), and 27% (15/56) in a phase II study (10) in patients with advanced or MCRC. However, it was a 3-week regimen of capecitabine (1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period) that was shown to have superior activity and improved safety over bolus 5-FU/LV (Mayo Clinic regimen) as the first-line therapy in two large randomized phase III studies (11–13), and has been approved for MCRC in Europe and in the United States. Since then, this 3-week regimen has been used as a platform for combination therapy with other active agents, such as irinotecan, oxaliplatin and bevacizumab (14–18).

To date, the efficacy and safety of the 3-week capecitabine regimen in Japan remains unclear. Therefore, we conducted this phase II trial as a registration trial, which included a pharmacokinetic analysis, of the 3-week capecitabine regimen in Japanese patients with previously untreated MCRC.

PATIENTS AND METHODS

STUDY DESIGN

The primary endpoint of this open-label multicenter phase II study was response rate. Secondary endpoints were safety, time-to-tumor progression (TTP), survival and pharmacokinetic analysis. This study was conducted in accordance with the Good Clinical Practice guidelines for clinical trials in Japan and the Declaration of Helsinki. The study protocol was approved by the ethics committee of each institution. Written informed consent was obtained from all patients.

PATIENTS

All patients had to have histologically confirmed colorectal adenocarcinoma with at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) (19). Patients were also required to have the following labor-

atory values: neutrophils $\geq 1.5 \times 10^3/mm^3$; platelet count $>10 \times 10^4/mm^3$; serum creatinine $<1.5 \times$ upper limit of normal (ULN); serum bilirubin $<1.5 \times$ ULN; ALT (GPT), AST (GOT) $\leq 2.5 \times$ ULN (or $\leq 5 \times$ ULN in the case of liver metastases); alkaline phosphatase $\leq 2.5 \times$ ULN (or $\leq 5 \times$ ULN in the case of liver metastases or $\leq 10 \times$ ULN in the case of bone disease) and creatinine clearance >50 ml/min. Patients had received no chemotherapy for metastatic disease (excluding adjuvant chemotherapy completed more than 6 months before registration) and no radiotherapy to target lesions. Patients were not included if they had received radiotherapy within the previous 4 weeks, or had not fully recovered from the major surgery within 4 weeks. Other eligibility criteria were as follows: Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; expected survival time of more than 3 months and age at enrollment of 20–74 years.

Exclusion criteria were as follows: pregnant or lactating women; sexually active men/women unwilling to practice contraception during the study; a history of hypersensitivity to 5-FU; organ allografts; clinically significant cardiac disease or myocardial infarction within the last 12 months; metastases of the central nervous system; a history of epilepsy; psychiatric disability precluding compliance with oral drug intake or giving informed consent; history of another malignancy within the last five years, except for cured basal cell carcinoma of skin, cured carcinoma *in situ* of uterine cervix, or cured esophago-gastric carcinoma removed by endoscopic procedures; serious uncontrolled infection; malabsorption syndrome; participation in any investigational drug study within 4 weeks preceding the start of treatment.

EVALUATION OF RESPONSE AND SAFETY

Anti-tumor efficacy was evaluated by the investigators according to RECIST guidelines (19). An Independent Review Committee (IRC) confirmed tumor responses. Adverse events were assessed according to the National Cancer Institute—Common Toxicity Criteria, Version 2.0 (20). Hand-foot syndrome (HFS) was classified as follows: grade 1 (numbness, dysesthesia, painless swelling or erythema not disrupting daily living activities); grade 2 (erythema with painful swelling or disruption of daily living activities) or grade 3 (moist desquamation, ulceration, blistering or severe pain, or any symptoms leading to an inability to work or to perform daily living activities).

STUDY ASSESSMENTS

Tumor responses were assessed every 2 cycles up to the cycle 10, and then every 3 cycles. Tumor markers (CEA and CA19-9) were also assessed at these times. Laboratory tests were performed before treatment, on day 8 of cycle 1 and on day 22 of each cycle. Drug compliance was reviewed at regular patient visits by checking unused tablets. Survival in all patients was monitored for 2 years after the last patient was enrolled.

DOSAGE AND DOSE MODIFICATIONS

Capecitabine (Xeloda®) 1250 mg/m² was taken orally twice daily within 30 min after breakfast and dinner. The actual dose of capecitabine administered was determined according to the patient's body surface area (BSA) as follows: 3000 mg/day if BSA was <1.33; 3600 mg/day if BSA was between 1.33 and 1.56; 4200 mg/day if BSA was between 1.57 and 1.80; and 4800 mg/day if BSA was >1.80. Each cycle of therapy consisted of 2 weeks of capecitabine administration followed by a 1-week rest period. Patients received treatment unless they had disease progression or unacceptable toxicity, or withdrew consent.

Treatment interruption or dose reductions were made if patients experienced grade 2–4 toxicities, but not if the toxicity was considered unlikely to become serious or life-threatening. Treatment was interrupted in cases of grade 2 or grade 3 toxicities and was not resumed until adverse drug reactions improved to grade 1. The dose of capecitabine was not reduced for the subsequent treatment cycle in cases of the first appearance of grade 2 toxicity. Capecitabine dose was reduced by 25% when patients experienced any grade 2 toxicity for a second time or for any grade 3 toxicity. It was reduced by 50% when patients experienced any grade 2 toxicity three times, any grade 3 toxicity twice, or any grade 4 toxicity. Treatment was discontinued if such toxicities were observed despite dose reduction.

STATISTICAL METHODS

The target number of patients for accrual was 60. Given an expected response rate of 25%, a threshold response rate of 10% and a one-tailed probability of 0.025, the statistical power was 80%. All eligible patients were included in the analysis of response. The 95% confidence interval (CI) of the response rate was calculated by the exact method, assuming a binomial distribution of data. Treatment duration was defined as days from the first day of drug administration to the last regulated rest day of the final cycle. Dose intensity was calculated by dividing the cumulative dose/treatment duration by BSA. TTP was calculated as the time from the first administration of capecitabine to disease progression or death if the patient died before progression. Overall survival was defined as the time from study enrolment to death. These endpoints were calculated by the Kaplan–Meier method. Safety was evaluated in all patients who received capecitabine treatment.

PHARMACOKINETIC ANALYSIS

Blood sampling was performed in the first 20 patients who gave consent to participate in the pharmacokinetic study. On day 1, the evening dose of capecitabine was not administered in order to quantify urinary recovery of capecitabine and its metabolites over a 24 h collection period. On days 1 and 14, 5 ml blood samples were collected at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8 and 11 h after the morning dose using vacutainers containing EDTA as an anticoagulant. Blood samples were centrifuged at 1500 g and 4°C for 10 min, and supernatant plasma was

removed and stored in plastic tubes below −20°C until analysis. Urine was collected and pooled during the following time intervals: 0, 0–11 and 11–24 h on day 1; and 0–11 h on day 14. At the end of each interval, the total volume and the pH of urine were recorded; and a 15 ml aliquot was removed and stored at −20°C until analysis.

Plasma and urine concentrations of capecitabine and its metabolites were determined by a validated liquid chromatography with mass-spectrometry detection (LC/MS-MS). The lower limits of quantification (LLOQ) of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and α-fluoro-β-alanine (FBAL) in plasma were 0.01, 0.01, 0.05, 0.002 and 0.011 μg/ml, respectively. The LLOQ of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU, α-fluoro-β-ureidopropionic acid and FBAL in urine were 0.02, 0.02, 0.02, 0.1, 0.02 and 0.1 μg/ml, respectively.

Pharmacokinetic parameters were assessed by standard non-compartment analysis, using WinNonlin® professional version 4.1 (Pharsight Corporation). Maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were determined. Apparent half-life $(t_{1/2})$ was estimated from ln2/λ, where the apparent rate constant of elimination, λ, was estimated by linear regression on the logarithm of the plasma concentration versus time data. The area under the plasma concentration time curve from time 0 to infinity (AUC) was estimated from the sum of AUC_{0-t} and C_{tlast}/λ, where AUC_{0-t} is the area under the curve from time 0 to the last sampling time (t_{last}) at which a concentration above the limit of quantification was measured (C_{tlast}). AUC_{0-t} was estimated using the linear-log trapezoidal rule. Percentage of dose recovered in urine as capecitabine or one of its metabolites was calculated based on the dose administered, urinary concentration and volume of urine collected.

RESULTS

PATIENT CHARACTERISTICS

Sixty patients were enrolled at 11 centers between January 2003 and November 2003. All patients met the eligibility criteria and received at least one dose of capecitabine. Therefore, both tumor response and safety were assessed in 60 patients. The baseline characteristics of patients are shown in Table 1. Median age was 60 years (range 34–71 years). A total of 33 patients (55%) had colon cancer, and 26 (43%) had rectal cancer. Metastatic sites affected were liver (73%), lung (58%), lymph node (47%) and others (17%).

TREATMENT DURATION AND INTENSITY

The median duration of treatment was 186 days (range 8–508 days). The median cumulative dose of capecitabine was 370 g (range 27–1255 g). The planned dose intensity was 1667 mg/m²/day and the actual median dose intensity was 1420 mg/m²/day (range 940–2220 mg/m²/day). Approximately 57 and 35% of patients completed 8 and 10 cycles of therapy, respectively. The reasons for treatment discontinuation were progressive disease (54 patients), adverse reactions (5 patients) and salvage surgical therapy (1 patient).

Table 1. Baseline patient demographics (intent-to-treat population)

Parameter	No. of patients	%
No. patients enrolled	60	100
Sex		
Male	33	55
Female	27	45
Age (years)		
Median	60	
Range	34–71	
Primary site		
Colon	33	55
Rectum	26	43
Colon/rectum	1	2
ECOG performance status		
0	42	70
1	17	28
2	1	2
Metastatic sites		
Liver	44	73
Lung	35	58
Lymph node	28	47
Other	10	17
Number of metastatic sites		
1	18	30
2	31	52
≥3	11	18
Resection		
Yes	54	90
No	6	10
Prior radiotherapy	1	2
Prior 5-FU or 5-FU analog-based adjuvant chemotherapy	10	17

The median dose per cycle was >75% of the planned dose up to 10 cycles.

EFFICACY

The objective response rate according to the IRC assessment was 35% (95% CI, 23–48%) (Table 2). Twenty-one patients had a partial response, and 31 (52%) had stable disease. Partial responses were observed in 11 out of 44 patients (25%) with liver metastases, 14 out of 35 patients (40%) with lung metastases and in 8 out of 28 patients (29%) with lymph nodes metastases. The median TTP was 5.5 months (95% CI, 4.2–6.7 months) (Fig. 1). Survival follow-up was performed at the cut-off date of October 2005. Thirty-five patients died of disease progression and there were no treatment-related deaths. The median overall survival was 20.2 months

Table 2. Tumor responses (N = 60)

Response	No. of patients (%)	
	Assessed by investigators	Confirmed by Independent Review Committee
Complete response (CR)	0 (0)	0 (0)
Partial response (PR)	19 (32)	21 (35)
Stable disease (SD)	33 (55)	31 (52)
Progressive disease (PD)	7 (12)	8 (13)
Not evaluable	1 (2)	0 (0)
Overall response rate	32% (95% CI, 20–45%)	35% (95% CI, 23–48%)
Disease control (CR + PR + SD)	87% (95% CI, 75–94%)	87% (95% CI, 75–94%)

CI: confidence interval.

(95% CI, 16.6–27.8 months) and the 1-year survival rate was 70% (Fig. 1).

SAFETY

The common adverse drug reactions (all grades) were HFS (73%), pigmentation (38%), diarrhea (37%), anorexia (37%), nausea (37%) and stomatitis (37%) (Fig. 2). The most frequent grade 3/4 adverse drug reaction was HFS (13%), but it was managed relatively easily by treatment interruption or dose reduction. No grade 4 diarrhea was observed, and grade 3 diarrhea was seen in only one patient. Ileus occurred in one patient. As for grade 3/4 laboratory abnormalities, the common events were elevated total bilirubin (12%) and elevated AST (10%). One patient had grade 3 leucopenia, and 5 patients had grade 3 neutropenia. One patient had grade 4 hyperglycemia.

Treatment was interrupted due to adverse drug reactions in 48 patients (80%). The median time to the first interruption was 43 days. The major cause of treatment interruption was HFS (25 patients). Dose reduction was needed in 32 patients (53%), and 10 patients had the second dose reduction. The median time to the first dose reduction was 78 days, and to second dose reduction was 162 days. Nineteen patients had dose reductions due to HFS. Five patients discontinued treatment because of adverse events: ileus (grade 4, treatment related); hepatitis C (grade 3, not related, an accidental acute infection); liver function abnormality (grade 2, not related, due to the progression of liver metastasis); hydronephrosis (grade 4, not related) and HFS (grade 3, treatment related).

PHARMACOKINETICS

Plasma concentrations for capecitabine and its metabolites (5'-DFCR, 5'-DFUR, 5-FU and FBAL) are shown in Fig. 3. The pharmacokinetic parameters are summarized in Table 3. Peak plasma concentrations of capecitabine and its metabolites