week cycle. The minimum requirements for the initiation of consolidation chemotherapy were as follows: leukocyte count 4000/μl or more, neutrophil count 2000/μl or more, platelet count 100000/μl or more, and nonhematological toxicity grade 2 or less.

During the entire treatment period, granulocyte colony-stimulating factor (G-CSF) support was used if the leukocyte count was below 1000/μl, neutrophil count was below 500/μl, or febrile neutropenia (<1000/μl) was noted.

### TRT

TRT was delivered concurrently with weekly chemotherapy, starting on day 1. The prescribed dose was 60 Gy in 30 fractions (2.0 Gy per fraction) over 6 weeks. Irradiation was performed with 10-MV photons from a linear accelerator. The radiation field was defined as the area that contained the primary tumor, a margin of 15 mm, the bilateral upper mediastinal lymph nodes, the subcarinal lymph nodes, and the enlarged regional lymph nodes. After initial irradiation at a dose of 40 Gy, off-cord (i.e., the spinal cord was outside the field) oblique boost fields were used. The boost field contained the same lymph nodes as the initial field. No correction for lung attenuation was made.

TRT was suspended if any of the following toxicities was noted: leukocyte count less than 1000/μl, neutrophil count less than 500/μl, febrile neutropenia (<1000/μl), platelet count less than 10000/μl, thrombopenia requiring platelet transfusion, esophagitis grade 3 or more, or pneumonitis grade 1 or more.

### Toxicity and response evaluation

A complete medical history was obtained, and physical examination was performed. Staging procedures consisted of chest X-ray; computed tomographic (CT) scans of the chest, brain, and upper abdomen; bone scintigraphy; and bronchoscopy. The following laboratory tests were carried out: complete blood count (CBC) with differential count of leukocytes, blood biochemistry, tumor marker, arterial blood gas analysis, urinalysis, electrocardiogram, and pulmonary function test.

During the treatment, the following tests were performed: CBC, twice a week; blood biochemistry, arterial blood gas analysis (during TRT), urinalysis, and chest X-ray, once a week; and chest CT scan for response evaluation, once a month.

Toxicity was graded according to the National Cancer Institute-Common Toxicity Criteria version 2, published in 1998.[16] In this study, we defined DLTs as the following toxicities; leukocyte count less than 1000/μl, neutrophil count less than 500/μl, febrile neutropenia (<1000/μl), platelet count less than 10000/μl, thrombopenia requiring platelet transfusion, nonhematological toxicity of grade 3 or more (except for nausea and vomiting), or any toxicity that required treatment interruption lasting more than 2 weeks.

Response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST).[17] A complete response (CR) was defined as the disappearance of all target lesions. A partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameters of target lesions for at least 4 weeks without the appearance of new lesions. Progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameters of target lesions, or the appearance of one or more new lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

The survival curve was drawn using the Kaplan-Meier method.[18]

**Table 1.** Dose setting

| Dose level | Cisplatin ($mg/m^2$ per week) | Vinorelbine ($mg/m^2$ per week) |
|---|---|---|
| 0 | 20 | 10 |
| 1 | 20 | 15 |
| 2 | 20 | 20 |

### Dose setting

Commonly, cisplatin is administered at 80 $mg/m^2$ every 3 or 4 weeks for advanced NSCLC, so the dose of cisplatin was fixed at 20 (= 80/4) $mg/m^2$ per week. We planned the dose escalation of vinorelbine, of which the starting dose was 15 $mg/m^2$ per week (dose level 1) with a 5 $mg/m^2$ per-week increment (Table 1). Three patients were treated initially at the starting dose level. If no patients experienced a DLT, the dose of vinorelbine was to be escalated. If one or two patients experienced a DLT, three additional patients were to be enrolled at the same dose level. If one or two of the six patients experienced a DLT, dose escalation was to be continued. If three or more patients experienced a DLT, that dose was to be considered as the MTD. The recommended dose was defined as the dose that immediately preceded the MTD. Although our plan was to carry out a dose-escalation study, as described above, the dose of vinorelbine was actually reduced, due to unacceptable toxicity. Details are described later.

For the patients who experienced a DLT, the dose of subsequent chemotherapy was reduced by one dose level or omitted if they had been given dose level 0.

## Results

### Patient characteristics

From March 2001 to April 2002, nine patients were enrolled in this study. Patient characteristics are listed in Table 2. The study population consisted of eight men and one woman with a median age of 59 years. The majority had a performance status of one. There were four patients with stage IIIA disease and five with stage IIIB. The histologic

**Table 2.** Patient characteristics

| Characteristic | No. (%) [$n = 9$] |
|---|---|
| Sex | |
| Male | 8 (89) |
| Female | 1 (11) |
| Age, years | |
| Median | 59 |
| Range | 48–68 |
| Weight loss, % | |
| ≤10 | 8 (89) |
| >10 | 1 (11) |
| Performance status (ECOG) | |
| 0 | 1 (11) |
| 1 | 8 (89) |
| Stage | |
| IIIA | 4 (44) |
| IIIB | 5 (56) |
| Histology | |
| Adenocarcinoma | 3 (33) |
| Squamous cell carcinoma | 6 (67) |

**Table 3.** Toxicity profile

| Toxicity | Dose level 1 ($n = 3$) | | | | Dose level 0 ($n = 6$) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade | | | | Grade | | | |
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Hematological | | | | | | | | |
| Leukocytes | 1 | 1 | 0 | 0 | 0 | 3 | 3 | 0 |
| Neutrophils | 0 | 1 | 0 | 0 | 1 | 3 | 2 | 0 |
| Hemoglobin | 2 | 1 | 0 | 0 | 4 | 2 | 0 | 0 |
| Platelets | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nonhematological | | | | | | | | |
| Esophagitis | 0 | 0 | 3 | 0 | 3 | 2 | 0 | 0 |
| Fatigue | 1 | 2 | 0 | 0 | 1 | 0 | 2 | 0 |
| Infection | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| Febrile neutropenia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyponatremia | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| Pneumonitis (acute) | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Pneumonitis (late) | 0 | 1 | 0 | 0 | 1 | 3 | 0 | 0 |
| AST/ALT | 1 | 1 | 0 | 0 | 2 | 0 | 0 | 0 |
| Creatinine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nausea | 1 | 0 | 1 | 0 | 0 | 2 | 2 | 0 |
| Vomiting | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

type was adenocarcinoma in three patients, and squamous cell carcinoma in six. The weight loss of all but one patient was less than 10%.

## Toxicity

First, we treated three patients at dose level 1, and all of them experienced grade 3 esophagitis. Therefore we decreased the dose of vinorelbine to dose level 0. One of the three patients at dose level 0 experienced grade 3 fatigue, infection, and hyponatremia. Three additional patients were enrolled at the same dose level. One of the three additional patients also experienced grade 3 fatigue, infection, and hyponatremia. Esophagitis, fatigue, infection, and hyponatremia were considered as the DLTs. All three patients at dose level 1 and two of the six patients at dose level 0 experienced DLTs. Therefore, dose level 1 was considered as the MTD, and dose level 0 as the recommended dose. Other nonhematological toxicities, such as pneumonitis, hepatic dysfunction, and nausea and vomiting, were mild to moderate. Hematological toxicity was not severe in any patients. No treatment-related death occurred. The toxicity profile is summarized in Table 3.

## Treatment delivery

In the four patients without DLT and one with DLT, weekly chemotherapy and TRT were administered according to the planned dosing schedule. In four patients with DLT, dose reduction or omission of chemotherapy was necessary. In three patients with DLT, TRT was completed with an interruption of 10 to 13 days. In one patient with DLT, TRT was discontinued at 54 Gy.

Consolidation chemotherapy was administered in seven patients. All received the combination of cisplatin and vinorelbine. In six of the seven patients, the initiation of consolidation chemotherapy was delayed due to esophagitis, leukopenia, or neutropenia.

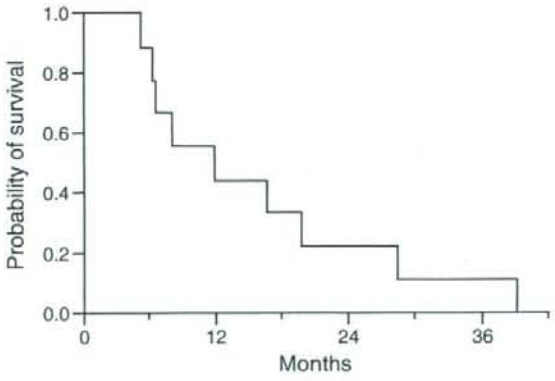


**Fig. 2.** Overall survival

## Response and survival

There were five PRs and no CRs, with a response rate of 56% (95% confidence interval, 21% to 86%). All three patients at dose level 1 and two of the six patients at dose level 0 responded.

All patients were followed up to death. The median overall survival was 11.9 months, with a 1-year survival rate of 44% (Fig. 2). The median time to progression was 7.8 months. The initial relapse site was local progression in six patients and distant metastasis in three.

## Discussion

Some randomized trials and meta-analyses have shown that the combination of chemotherapy and TRT has survival benefits compared with TRT alone for locally advanced NSCLC.[12,19-26] However, long-term survival was rare, with a median survival of 12 to 13.7 months and a 5-year survival rate of only 8% to 17%.

The West Japan Lung Cancer Group conducted a phase III study to compare concurrent chemoradiotherapy with sequential therapy.[27] The chemotherapy consisted of cisplatin, vindesine, and mitomycin, and TRT delivered a total of 56 Gy. The median survival in the concurrent arm was significantly longer than that in the sequential arm (16.5 versus 13.3 months). The Radiation Therapy Oncology Group (RTOG) and a Czech group conducted similar randomized trials and confirmed the superiority of the concurrent therapy over the sequential therapy.[28,29] Furthermore, Choy et al.[30] conducted a randomized phase II study of three regimens: sequential chemoradiotherapy versus induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy followed by consolidation chemotherapy; this was the so-called locally advanced multimodality protocol (LAMP) study. They used the combination of paclitaxel, carboplatin, and TRT. The median survival was 12.5 months for the sequential arm, 11 months for the induction/concurrent arm, and 16.1 months for the concurrent/consolidation arm. These results suggested that concurrent chemoradiotherapy, or possibly concurrent chemoradiotherapy followed by consolidation chemotherapy, was the most effective treatment in patients with locally advanced NSCLC. However, it is undetermined what regimen or what schedule is optimal for chemoradiotherapy.

Several schedules and doses of cisplatin, vinorelbine, and concurrent TRT have been reported. Masters et al.[31] recommended that cisplatin should be administered at 80 mg/m$^2$ on day 1 and vinorelbine at 15 mg/m$^2$ on days 1 and 8 every 3 weeks with standard TRT. After that, the Cancer and Leukemia Group B (CALGB) performed a randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy.[32] In the cisplatin-vinorelbine arm, the doses reported by Masters et al.[31] were used, and the CALGB concluded that induction chemotherapy followed by concomitant chemoradiotherapy was feasible, with the observed survival rates exceeding those of previous CALGB trials for all treatment arms. Sekine et al.[33] conducted a phase I study and reported that the recommended dose of cisplatin was 80 mg/m$^2$ on day 1 and that of vinorelbine was 20 mg/m$^2$ on days 1 and 8 every 4 weeks with TRT including a 4-day interval. The Czech group[29] used the following schedule and dose: cisplatin 80 mg/m$^2$ on day 1 and vinorelbine 12.5 mg/m$^2$ on days 1, 8, and 15 every 4 weeks with standard TRT starting on day 4.

Although the frequent interaction of anticancer agents and irradiation may produce stronger radio-sensitizing effects, there has been no report of a weekly schedule to date. Therefore we conducted a phase I study of weekly cisplatin and vinorelbine with standard TRT. The studies described above[29,31-33] reported that esophagitis and neutropenia were the major toxicities. The present study showed that the DLTs of our regimen were esophagitis, fatigue, infection, and hyponatremia. All patients at dose level 1 experienced grade 3 esophagitis, so this dose was considered an overdose. The strong radio-sensitizing effects may have resulted in the severe esophagitis. On the other hand, no severe neutropenia was observed. The recommended dose of cisplatin is 20 mg/m$^2$ per week and that of vinorelbine is 10 mg/m$^2$ per week in the present study.

The response rate and the median overall survival in this study were 56% and 11.9 months, respectively. Some concurrent chemoradiotherapy studies have reported better results, with response rates of 63% to 85% and median overall survivals of 11 to 18.3 months.[12,27-30,32] As our study had a very small sample size, of only nine patients, we cannot draw conclusions on the efficacy of this treatment from our present results.

In conclusion, our phase I study of weekly cisplatin, vinorelbine, and concurrent TRT showed that the DLTs of this treatment were esophagitis, fatigue, infection, and hyponatremia. The recommended dose of cisplatin is 20 mg/m$^2$ per week and that of vinorelbine is 10 mg/m$^2$ per week, i.e., on days 1, 8, 15, 22, 29, and 36, with standard TRT. We believe a phase II study of this treatment is warranted.

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

## *West Japan Thoracic Oncology Group (WJTOG) 0104*

**Nobuyuki Yamamoto, MD**
**Kazuhiko Nakagawa, MD**
**Hisao Uejima, MD**
**Takahiko Sugiura, MD**
**Yoshiki Takada, MD**
**Shun-ichi Negoro, MD**
**Kaoru Matsui, MD**
**Tatsuhiko Kashii, MD**
**Minoru Takada, MD**
**Yoichi Nakanishi, MD**
**Terufumi Kato, MD**
**Masahiro Fukuoka, MD**

Department of Thoracic Oncology, Shizuoka Cancer Center, Naga-izumi, Japan.

This study was conducted under the auspices of the West Japan Thoracic Oncology Group.

Address for reprints: Nobuyuki Yamamoto, MD, Thoracic Oncology Division, Shizuoka Cancer Center Hospital, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8777, Japan; Fax: (011) 81 559895634; E-mail: n.yamamoto@scchr.jp

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

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

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

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

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

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


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

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

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

## MATERIALS AND METHODS

### Patient Selection

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

### Randomization and Treatment Plan

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

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

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

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

It was acceptable to administer a 5-hydroxytriptamine receptor antagonist and/or dexamethasone intravenously before the start of chemotherapy to prevent nausea and emesis. The use of granulocyte-colony stimulating factors was not allowed during treatment except in patients who had Grade 4 leukopenia, Grade 4 neutropenia, or febrile neutropenia, according to the investigator's decision. Transfusions of red blood cells and platelets were allowed in patients who had Grade $\geq$3 anemia and in patients who had platelet counts $\leq$20,000/$\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 $\geq$1 new lesion(s). Stable disease (SD) was defined as neither sufficient shrinkage to qualify for a PR nor a sufficient increase to qualify for PD for a minimum of 6 weeks. Response duration in patients who achieved a CR or PR was measured from the start of treatment to the date of disease progression.

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

### Statistical Methods

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

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

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

TABLE 1
Baseline Patient Characteristics

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

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

## RESULTS

### Patient Characteristics

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

### Treatment Delivery

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

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

TABLE 2
Treatment Delivery and Dose Reduction Rate

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

### Treatment Response and Survival

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

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

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

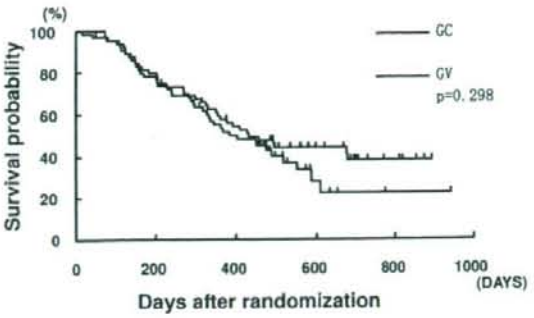


**FIGURE 1.** Overall survival is illustrated for the 2 treatment arms. GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.

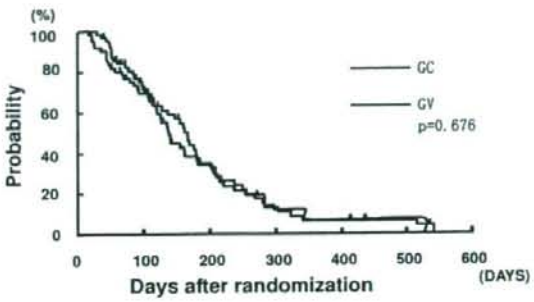


**FIGURE 2.** Progression-free survival is illustrated for the 2 treatment arms. GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.

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

### Toxicity

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

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

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

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

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

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

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

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

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

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

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

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

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

## DISCUSSION

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

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

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

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

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

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

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

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

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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)

*Shinzoh Kudoh, Koji Takeda, Kazuhiko Nakagawa, Minoru Takada, Nobuyuki Katakami, Kaoru Matsui, Tetsu Shinkai, Toshiyuki Sawa, Isao Goto, Hiroshi Semba, Takashi Seto, Masahiko Ando, Taroh Satoh, Naruo Yoshimura, Shunichi Negoro, and Masahiro Fukuoka*

From the Department of Respiratory Medicine, Osaka City University Medical School; Department of Medical Oncology, Osaka City General Hospital; Department of Medical Oncology, Kinki University Medical School; Department of Respiratory Medicine, Rinku General Medical Center; Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases; Department of Respiratory Medicine, Osaka Medical College, Osaka; Division of Respiratory Medicine, Kobe City General Hospital, Kobe; Department of Internal Medicine, Shikoku Cancer Center, Ehime; Department of Respiratory Medicine, Gifu Municipal Hospital, Gifu; Department of Internal Medicine, Kumamoto Regional Medical Center, Kumamoto; and the Health Service, Kyoto University, Kyoto, Japan.

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Address reprint requests to Shinzoh Kudoh, MD, Department of Respiratory Medicine, Osaka City University Medical School, 1-4-3, Asahimachi, Abeno-ku, Osaka 545-8585, Japan; e-mail: shinzohykudoh@med.osaka-cu.ac.jp.



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## ABSTRACT

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

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

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

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

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## INTRODUCTION

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

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

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

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

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

## PATIENTS AND METHODS

### Eligibility Criteria

Chemotherapy- and radiotherapy-naive 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/$\mu$L or higher; absolute neutrophil count, 2,000/$\mu$L or higher; hemoglobin concentration, 9.5 g/dL or higher; platelet count, 100,000/$\mu$L 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/$\mu$L and lower than 50,000/$\mu$L, respectively, and was withheld until the counts had recovered to 4,000/$\mu$L or higher and 100,000/$\mu$L 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.

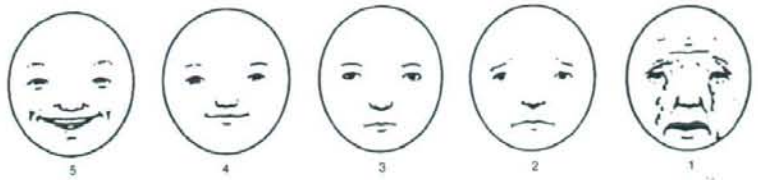
### Statistical Analysis

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 $\chi^2$ 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.

A




B

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

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

## RESULTS

### *Patient Characteristics*

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

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

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

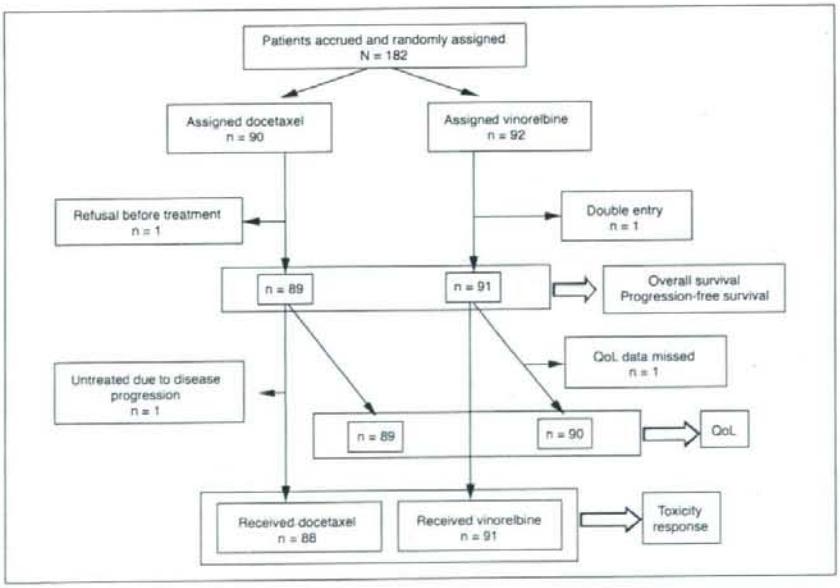



**Fig 2.** Flow diagram for the study. QoL, quality of life.

**Table 1.** Patient Characteristics

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

*A data was not obtained from one vinorelbine patient.

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

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

### Response and Survival

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

**Table 2.** Response to Treatment

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

NOTE. $P = .019$.

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

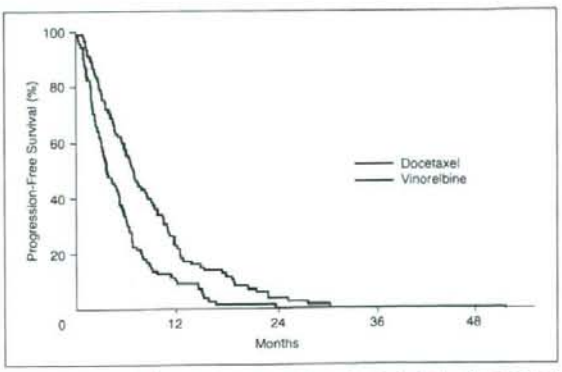



**Fig 3.** Progression-free survival curves for patients treated with docetaxel (n = 89) or vinorelbine (n = 91).

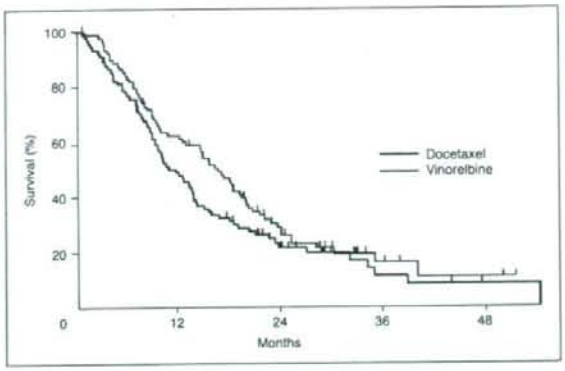



**Fig 4.** Overall survival curves for patients treated with docetaxel (n = 89) or vinorelbine (n = 91).

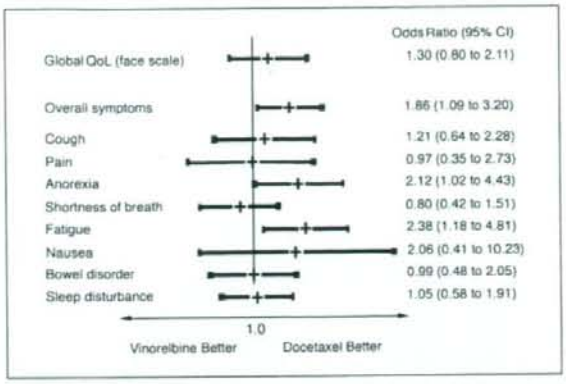



**Fig 5.** Forest plot of odds ratio for global quality of life (QoL) and disease-related symptoms analyses.

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

**Table 3.** Toxicities

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

NOTE. *P* values ware obtained by $\chi^2$ 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-naive NSCLC patients, which reported median survival times of 11.4 months to 14.8 months.[5] The improved overall survival time in the docetaxel arm may be attributed to gefitinib treatment as a second-line treatment. Japanese patients are sensitive to gefitinib, and 37% of patients who were treated with docetaxel also received gefitinib, compared with 20.9% of vinorelbine treated patients although this difference may be attributable to the numerically greater number of patients alive after initial docetaxel treatment. Crossover to second-line chemotherapy was permitted in this protocol and could have also influenced outcomes. However, as only a small number of patients in either treatment arm were treated with alternative chemotherapy as salvage (five patients from the docetaxel arm and nine patients from the vinorelbine arm), outcomes for these patients were not felt to significantly alter the overall results of the study.

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

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

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

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

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### Appendix

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

### Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

### Author Contributions

**Conception and design:** Shinzoh Kudoh, Koji Takeda, Kazuhiko Nakagawa, Shunichi Negoro, Masahiro Fukuoka
**Administrative support:** Shinzoh Kudoh, Kazuhiko Nakagawa, Minoru Takada, Taroh Satoh, Shunichi Negoro, Masahiro Fukuoka
**Provision of study materials or patients:** Shinzoh Kudoh, Koji Takeda, Kazuhiko Nakagawa, Minoru Takada, Nobuyuki Katakami, Kaoru Matsui, Tetsu Shinkai, Toshiyuki Sawa, Isao Goto, Hiroshi Semba, Takashi Seto, Taroh Satoh, Naruo Yoshimura
**Collection and assembly of data:** Kazuhiko Nakagawa, Takashi Seto, Masahiko Ando, Taroh Satoh, Naruo Yoshimura
**Data analysis and interpretation:** Shinzoh Kudoh, Koji Takeda, Kazuhiko Nakagawa, Minoru Takada, Nobuyuki Katakami, Kaoru Matsui, Tetsu Shinkai, Toshiyuki Sawa, Isao Goto, Hiroshi Semba, Takashi Seto, Masahiko Ando, Taroh Satoh, Naruo Yoshimura
**Manuscript writing:** Shinzoh Kudoh, Masahiko Ando
**Final approval of manuscript:** Shunichi Negoro, Masahiro Fukuoka

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

**K Nakagawa*[,1], S Kudoh[2], K Matsui[3], S Negoro[4,8], N Yamamoto[5], JE Latz[6], S Adachi[7,9] and M Fukuoka[1]**

[1]Kinki University School of Medicine, Osakasayama, 589-8511, Japan; [2]Osaka City University Medical School, Osaka, 545-8586, Japan; [3]Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Osaka, 583-8588, Japan; [4]Osaka City General Hospital, Osaka, 534-0021, Japan; [5]Shizuoka Cancer Center, Shizuoka, 411-8777, Japan; [6]Eli Lilly and Company, Indianapolis, IN, 46285, USA; [7]Eli Lilly Japan K.K., Kobe, 651-0086, Japan

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

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

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

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

*Correspondence: Dr K Nakagawa; E-mail: nakagawa@med.kindai.ac.jp
[8]Present address: Hyogo Medical Center for Adults, Akashi, 673-8558, Japan
[9]Present address: Eli Lilly and Company, Indianapolis, IN, 46285, USA
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thrombocytopenia, with or without grade 3/4 diarrhoea, mucositis, or infection. Homocysteine and methylmalonic acid are known as indicators of folate and vitamin $B_{12}$ deficiencies (Rosenberg and Fenton, 1989; Savage *et al*, 1994). Thus, it was hypothesized that a patient's risk for severe toxicity could be reduced by decreasing the levels of homocysteine and methylmalonic acid with folate and vitamin $B_{12}$ supplementation (FA/$VB_{12}$) (Niyikiza *et al*, 2002a).

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

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

## PATIENTS AND METHODS

### Patient selection

Eligible patients had histologic or cytologic diagnosis of solid cancer that was incurable by standard treatments. Patients also must have been between 20 and 75 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and have an estimated life expectancy of at least 3 months. Adequate organ function was required, which included bone marrow reserve (white blood cell count $4.0–12.0 \times 10^3$ $mm^{-3}$, platelets $\geqslant 100 \times 10^3$ $mm^{-3}$, haemoglobin $\geqslant 9.0$ g $dl^{-1}$, and absolute granulocyte count $\geqslant 2.0 \times 10^3$ $mm^{-3}$), hepatic function (bilirubin $\leqslant 1.5 \times$ upper limit of normal, aspartate/alanine transaminase (AST/ALT) $\leqslant 2.5 \times$ upper limit of normal, and serum albumin $\geqslant 2.5$ g $dl^{-1}$), renal function (serum creatinine $\leqslant$ upper limit of normal and Cockcroft and Gault creatinine clearance $\geqslant 60$ ml $min^{-1}$), and lung function (PaO2 $\geqslant 60$ torr).

Prior chemotherapy or hormone therapy was allowed if it was carried out $\geqslant 14$ days before study entry ($\geqslant 35$ days for nitrosourea or mitomycin-C). Previous radiotherapy was also allowed, but only if $\leqslant 25\%$ of marrow was irradiated and if it was completed $\geqslant 21$ days before study entry. Pretreated patients must have recovered from all toxicities before study entry. Prior surgery was allowed if patients recovered from the effect of the operation. Patients were excluded from this study for active infection, symptomatic brain metastasis, interstitial pneumonitis, or pulmonary fibrosis diagnosed by chest X-ray, serious concomitant systemic disorders incompatible with the study, clinically significant effusions, or the inability to discontinue aspirin and other nonsteroidal anti-inflammatory agents during the study.

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

### Treatment

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

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

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

### Dose escalation

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

A DLT was defined as the occurrence of one of the following toxicities during cycle 1: any grade 3/4 nonhematologic toxicity (except grade 3 nausea/vomiting and AST, ALT, or alkaline phosphatase elevation $<10 \times$ upper limit of normal that returns to grade 0–1 by the beginning of cycle 2), grade 3/4 febrile neutropenia ($<1000$ $mm^{-3}$ with $\geqslant 38.0$°C), grade 4 leucopenia ($<1000$ $mm^{-3}$) or neutropenia ($<500$ $mm^{-3}$) lasting $\geqslant 4$ days, thrombocytopenia ($<20\,000$ $mm^{-3}$), or thrombocytopenia ($\geqslant 20\,000$ $mm^{-3}$) requiring platelet transfusion. A failure to start the second cycle by day 42 owing to toxicity was also considered a DLT. All toxicities were assessed according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.

### Treatment assessments

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

### Pharmacokinetic analysis

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

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