duration of treatment with TSU-68 was 3 cycles (range, 1–18), with the median relative dose intensity being 75.9%. Eleven patients treated with TSU-68 at 400 mg twice daily had the dose reduced to 200 mg after a median of 2 cycles (range, 1–6): two each because of the development of thrombocytopenia of grade 4 or anorexia of grade 3, and one each because of hyponatremia of grade 4; an increase in alanine aminotransferase (ALT), diarrhea, pericarditis, fatigue, hyperkalemia, or febrile neutropenia of grade 3; or cholecystitis of grade 2.

Patient disposition is shown in Figure 1. Out of 34 patients, 19 individuals discontinued treatment before completion of combination therapy, most as a result of disease progression (six patients) or AEs (nine patients; four with neuropathy and one each with neuropathy and myalgia, with leukopenia, with pericarditis and pericardial effusion, or with an increase in aspartate aminotransferase or ALT). Fifteen patients completed four to six cycles of the combination therapy. The study treatment was discontinued in six of these patients because of disease progression (two patients) or AEs (four patients; two with leukopenia and neutropenia and one each with neuropathy or fatigue). The other nine patients continued TSU-68 monotherapy in a maintenance setting. TSU-68 was subsequently discontinued in eight of these nine patients because of disease progression and in the remaining patient because of an AE (infection of grade 2). No dose reductions of TSU-68 were implemented during maintenance therapy, which had a median duration of four cycles (range, 1–14).

Toxicity

The major AEs during the entire treatment period at the RD are shown in Table 2. The hematologic AEs of grade ≥3 included neutropenia (grade 3 in 35% of patients and grade 4 in 38%), anemia (grade 3 in 32% and grade 4 in 3%), thrombocytopenia (grade 3 in 24% and grade 4 in 9%), and leukopenia (grade 3 in 15% and grade 4 in 3%). Nonhematologic toxicities of grade 3 included neuropathy (9%), anorexia (15%), fatigue (6%), diarrhea (6%), and arthralgia, elevation of ALT or aspartate aminotransferase, edema (head and neck, or limb), and febrile neutropenia (each at 3%). No nonhematologic toxicities of grade 4 were observed, and there were also no treatment-related deaths.

Pharmacokinetics

Pharmacokinetic analysis of TSU-68, at doses of 200 mg ($n = 3$) and 400 mg ($n = 6$), in the presence of paclitaxel and carboplatin was performed in nine subjects. The increases in C_{max} and AUC for TSU-68 at level 2 (400 mg) on day 1 compared with those at level 1 (200 mg) were consistent with the increase in TSU-68 dosing (Table 3). At both doses, the plasma concentration of TSU-68 achieved C_{max} at 3 to 4 hours and then declined at a first-order rate (Figure 2). The C_{max} and AUC after repeated administration of TSU-68 on day 2 were lower than those after the first administration on day 1 (Figure 2, Table 3). The values for these pharmacokinetic parameters of TSU-68 administered with paclitaxel and carboplatin in this study are similar to those previously obtained for single-agent dosing of TSU-68. Pharmacokinetic analysis of paclitaxel and carboplatin-derived free platinum revealed that C_{max}, AUC, $t_{1/2}$, and Vd_{ss} did not differ substantially between the two dose levels of TSU-68 (Table 3).

TABLE 2. Adverse Events for 34 of the Study Patients

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Total (%)	Grade 3/4 (%)
Hematologic						
Hemoglobin	6	14	11	1	94.1	35.3
Neutrophils	0	4	12	13	85.3	73.5
Platelets	10	5	8	3	76.5	32.4
Leukocytes	6	12	5	1	70.6	17.6
Nonhematologic						
Neuropathy sensory	14	15	3	0	94.1	8.8
Alopecia	19	12	0	0	91.2	0
Anorexia	13	9	5	0	79.4	14.7
Nausea	13	14	0	0	79.4	0
Arthralgia	14	10	1	0	73.5	2.9
Fatigue	9	12	2	0	67.6	5.9
Diarrhea	11	9	2	0	64.7	5.9
Vomiting	12	9	0	0	61.8	0
Proteinuria	13	7	0	0	58.8	0
Myalgia	12	7	0	0	55.9	0
Edema: head and neck	12	0	1	0	38.2	2.9
ALT	9	2	1	0	35.3	2.9
AST	6	2	1	0	26.5	2.9
Edema: limb	4	1	1	0	17.6	2.9
Hypertension	3	4	0	0	20.6	0
Febrile neutropenia	0	0	1	0	2.9	2.9

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Biomarker Analysis

We investigated changes in blood biomarkers during treatment with TSU-68. The mean plasma levels of VEGF-C and E-selectin decreased significantly by 40 and 33%, respectively, from baseline levels over three cycles of treatment ($p < 0.001$) (Figure 3). The plasma concentration of soluble VEGFR2 also decreased by 13% from baseline after four cycles of treatment ($p < 0.05$). In contrast, the plasma levels of VEGF-A, PDGF-AA, PDGF-BB, acidic FGF, and basic FGF remained unchanged throughout treatment.

Antitumor Activity

A total of 33 of the 34 patients treated with 400 mg of TSU-68 twice daily combined with paclitaxel and carboplatin were assessable for response; the remaining patient was not available for measurement of target lesions. For the 33 assessable patients, there were 13 PRs and no CRs, yielding an overall response rate of 39.4% (95% confidence interval [CI], 22.9–57.9%). Thirteen patients (39.4%) had SD, yielding an overall disease control rate (CR + PR + SD) of 78.8% (95% CI, 61.1–91.0%). A waterfall plot revealed that most patients showed a decrease in the size of their target lesions (Figure 4). Median PFS was 5.6 months (95% CI, 3.6–7.2 months).

TABLE 3. Pharmacokinetic Parameters of TSU-68, Carboplatin (Free Platinum), and Paclitaxel After Drug Coadministration

(a) TSU-68

Level	t_{max} (h)	C_{max} (μg/mL)	$AUC_{0\text{-last}}$ (μg · h/mL)	$t_{1/2}$ (h)
1				
Day 1	3.0 ± 0.9	8.7 ± 0.9	42.5 ± 15.6	3.7 ± 0.5
Day 2	2.5 ± 1.5	6.1 ± 1.3	25.6 ± 6.3	3.2 ± 0.3
2				
Day 1	3.8 ± 1.0	14.6 ± 7.5	76.3 ± 35.9	2.4 ± 0.4
Day 2	3.2 ± 2.0	7.0 ± 3.0	35.6 ± 13.3	2.2 ± 0.8

(b) Carboplatin (Free Platinum)

Level	t_{max} (h)	C_{max} (μg/mL)	$AUC_{0\text{-last}}$ (mg · min/mL)	$AUC_{0\text{-inf}}$ (mg · min/mL)	$t_{1/2}$ (h)	CL_{tot} (mL/min)	Vd_{ss} (L)
1	1.0 ± 0.1	24.9 ± 4.8	4.12 ± 0.59	4.14 ± 0.59	3.9 ± 0.1	86.9 ± 16.3	15.8 ± 3.6
2	1.0 ± 0.1	24.5 ± 6.7	3.94 ± 0.62	3.98 ± 0.64	4.1 ± 0.4	96.1 ± 30.8	17.1 ± 2.6

(c) Paclitaxel

Level	t_{max} (h)	C_{max} (μg/mL)	$AUC_{0\text{-inf}}$ (μg · h/mL)	$AUC_{0\text{-inf}}$ (μg · h/mL)	$t_{1/2}$ (h)	CL_{tot} (mL min^{-1} m^{-2})	Vd_{ss} (L/m^2)
1	3.1 ± 0.1	6.50 ± 0.76	23.0 ± 1.7	23.3 ± 1.6	10.9 ± 0.7	143 ± 10	41.1 ± 11.0
2	3.1 ± 0.1	9.95 ± 3.33	29.9 ± 7.2	30.3 ± 7.2	10.7 ± 1.2	115 ± 25	33.6 ± 7.9

Data are presented as means ± SD (level 1, $n = 3$; level 2, $n = 6$).

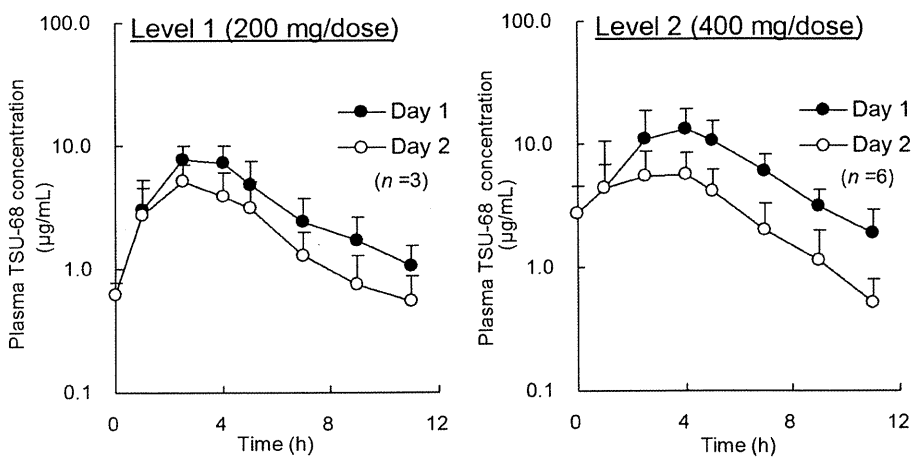

FIGURE 2. Time course of the plasma concentration of TSU-68 after administration of the first (day 1) or third (day 2) dose of the drug at 200 or 400 mg. Carboplatin and paclitaxel were coadministered on day 1. Data were presented as means ± SD.

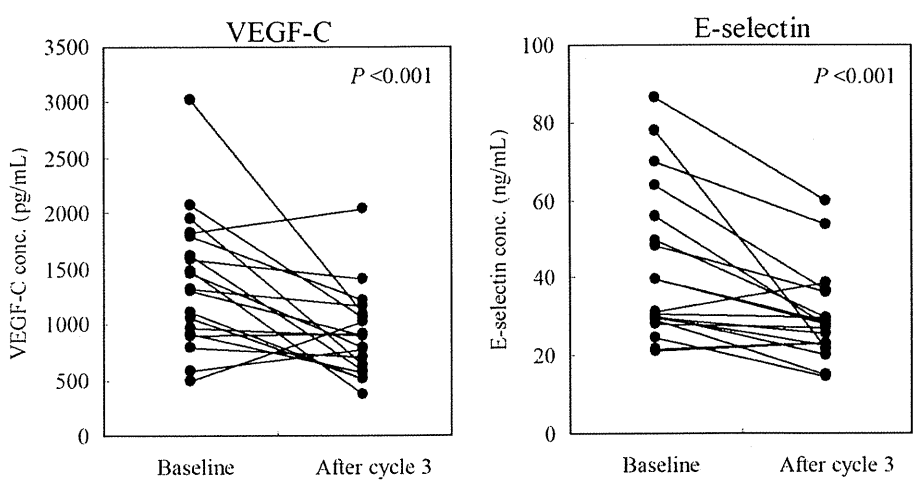

FIGURE 3. Changes in the plasma concentrations of biomarkers during treatment with TSU-68 in combination with carboplatin-paclitaxel chemotherapy. The plasma levels of VEGF-C and E-selectin were measured at baseline and after administration of three cycles of treatment for 19 patients. *p* values were determined with the paired exact Wilcoxon test (unadjusted).

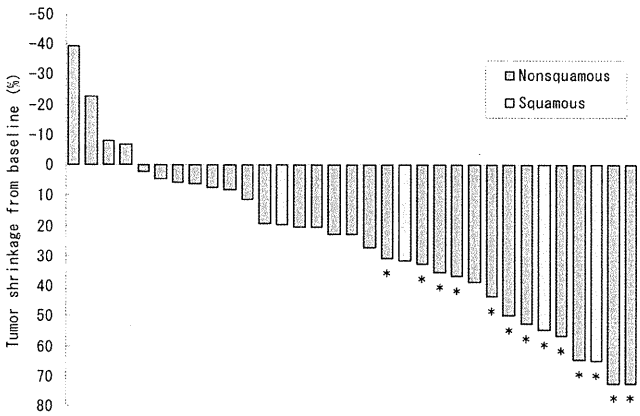

FIGURE 4. Tumor response. Maximal tumor shrinkage from baseline was determined for the 33 evaluable patients. Those showing a PR are indicated by asterisks.

DISCUSSION

Our phase I study was designed to evaluate the feasibility of daily administration of TSU-68 in combination with paclitaxel and carboplatin and thereby to identify a regimen suitable for further phase II and III evaluation in chemotherapy-naive individuals with advanced NSCLC. According to the criteria defined in our study, TSU-68 at a dose of 400 mg twice daily can be integrated with the combination of paclitaxel and carboplatin. Given that a previous phase I study established 400 mg twice daily as an appropriate dose for treatment with TSU-68 as a single agent,[14] further dose-escalation evaluation of this drug was not pursued. The AEs observed in this study were predictable from the safety profiles of TSU-68, carboplatin, and paclitaxel. Although there are limitations to comparisons of the results from different studies, the addition of TSU-68 to carboplatin and paclitaxel seems to increase the frequency and severity of thrombocytopenia and anemia compared with those previously observed with similar doses of carboplatin and paclitaxel.[5,17,18] With regard to nonhematologic toxicities, TSU-68 may increase the frequency of neuropathy and gastrointestinal conditions (diarrhea and nausea); however, most of these toxicities were of grade 1 or 2 and were manageable with standard supportive treatment. Other toxicities attributed to carboplatin-paclitaxel chemotherapy did not occur in this study at a greater rate or severity than expected. In contrast to other VEGFR tyrosine kinase inhibitors, no hand-foot syndrome and only a low frequency of hypertension were observed in the present trial, consistent with the safety data from other TSU-68 studies.[14,15] Importantly, none of the patients enrolled in this study, including those with squamous cell carcinoma, showed any bleeding events irrespective of relatedness. The small sample size of 37 patients treated with TSU-68 in this study makes it difficult to conclude whether the absence of life-threatening hemoptysis was attributable to chance. However, unlike bevacizumab, TSU-68 combined with carboplatin-paclitaxel seems to be safe for patients with all histological types of NSCLC.

The pharmacokinetics of TSU-68 administered with carboplatin and paclitaxel were found to be similar to those previously described for monotherapy.[14] The repeated administration of TSU-68 decreased its plasma exposure, as has been consistently observed in previous trials, possibly as a result of autoinduction of TSU-68 metabolism.[14,15,19] The pharmacokinetic parameters of carboplatin and paclitaxel did not differ substantially between the two tested doses of TSU-68. The pharmacokinetic parameters of paclitaxel and carboplatin in this study were similar to those previously described for respective single-agent administration.[20–22] Together, our pharmacokinetic data suggest that concomitant administration of TSU-68, carboplatin, and paclitaxel according to the adopted treatment schedule had no marked impact on the pharmacokinetics of any of the three drugs, although further well-designed pharmacokinetic studies will be necessary to accurately evaluate drug-drug interactions.

Evaluation of novel targeted agents is facilitated by the identification of biomarkers of biologic activity. E-selectin is an endothelial cell-specific membrane glycoprotein that participates in leukocyte adhesion and has also been suggested to function in angiogenesis.[23,24] VEGF-C, which is one of the ligands of VEGFR2 and VEGFR3, is active in angiogenesis and lymphangiogenesis.[25] We observed decreases in the plasma concentrations of E-selectin, VEGF-C, and soluble VEGFR2 associated with TSU-68 treatment, with similar findings having been described for other VEGF signaling inhibitors.[26–28] These observations may be related to the pronounced antiangiogenic activity of TSU-68 previously demonstrated in preclinical studies,[8,9] although the mechanism responsible for these effects remains unclear. Given that TSU-68 also inhibits PDGFR and FGFR as well as VEGFR, we also determined the plasma concentrations of PDGF-AA, PDGF-BB, acidic FGF, and basic FGF. However, there were no marked changes in the concentrations of these growth factors during TSU-68 treatment. Further attempts to identify potential biomarkers associated with inhibition of PDGFR and FGFR are warranted.

Although tumor evaluation was not the primary objective of our study, we found the chosen drug combination to be active, with a response rate of 39.4%, disease control rate of 78.8%, and median PFS of 5.6 months. These efficacy data compare favorably with those obtained in previous phase III studies of carboplatin and paclitaxel for chemonaive patients with advanced NSCLC,[5,17,18] suggesting that TSU-68 may augment the antitumor effects of chemotherapy.

In conclusion, administration of TSU-68 at 400 mg twice daily can be combined with a standard regimen of carboplatin-paclitaxel, without relevant pharmacokinetic interactions, in chemonaive patients with advanced NSCLC. The observed antitumor activity was encouraging, with most patients treated at the RD showing some degree of tumor shrinkage. Further studies of this triple-drug combination in patients with advanced NSCLC of any histology are thus warranted.

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Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 953–959, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2011.01.008

CLINICAL INVESTIGATION **Thoracic Cancer**

PHASE I STUDY OF CONCURRENT HIGH-DOSE THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY WITH CHEMOTHERAPY USING CISPLATIN AND VINORELBINE FOR UNRESECTABLE STAGE III NON-SMALL-CELL LUNG CANCER

IKUO SEKINE, M.D., PH.D.,* MINAKO SUMI, M.D.,PH.D.,† YOSHINORI ITO, M.D.,† HIDEHITO HORINOUCHI, M.D.,* HIROSHI NOKIHARA, M.D., PH.D.,* NOBORU YAMAMOTO, M.D., PH.D.,* HIDEO KUNITOH, M.D., PH.D.,* YUICHIRO OHE, M.D., PH.D.,* KAORU KUBOTA, M.D., PH.D.,* AND TOMOHIDE TAMURA, M.D.*

*Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; and †Division of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan

Purpose: To determine the maximum tolerated dose in concurrent three-dimensional conformal radiotherapy (3D-CRT) with chemotherapy for unresectable Stage III non–small-cell lung cancer (NSCLC).

Patients and Methods: Eligible patients with unresectable Stage III NSCLC, age ≥20 years, performance status 0–1, percent of volume of normal lung receiving 20 GY or more (V_{20}) ≤30% received three to four cycles of cisplatin (80 mg/m^2 Day 1) and vinorelbine (20 mg/m^2 Days 1 and 8) repeated every 4 weeks. The doses of 3D-CRT were 66 Gy, 72 Gy, and 78 Gy at dose levels 1 to 3, respectively.

Results: Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were enrolled at dose levels 1 to 3, respectively. The main reasons for exclusion were V_{20} >30% (n = 10) and overdose to the esophagus (n = 8) and brachial plexus (n = 2). There were 26 men and 5 women, with a median age of 60 years (range, 41–75). The full planned dose of radiotherapy could be administered to all the patients. Grade 3–4 neutropenia and febrile neutropenia were noted in 24 (77%) and 5 (16%) of the 31 patients, respectively. Grade 4 infection, Grade 3 esophagitis, and Grade 3 pulmonary toxicity were noted in 1 patient, 2 patients, and 1 patient, respectively. The dose-limiting toxicity was noted in 17% of the patients at each dose level. The median survival and 3-year and 4-year survival rates were 41.9 months, 72.3%, and 49.2%, respectively.

Conclusions: 72 Gy was the maximum dose that could be achieved in most patients, given the predetermined normal tissue constraints. © 2012 Elsevier Inc.

Lung cancer, Chemotherapy, Radiotherapy, High dose, Conformal.

INTRODUCTION

Approximately one third of patients with non–small-cell lung cancer (NSCLC) present with locally advanced Stage III disease at the initial diagnosis (1). Of this category, Stage IIIA disease with bulky N2 and Stage IIIB disease without pleural effusion are characterized by a large primary lesion and/or involvement of the mediastinal or supraclavicular lymph nodes. In addition, the majority of these patients have occult systemic micrometastases. Concurrent thoracic radiotherapy and chemotherapy has been the standard care for these patients with unresectable disease (2, 3). A platinum doublet with a third-generation anticancer agent combined with thoracic radiotherapy was reported to yield a median overall survival time (OS) of more than 2 years and long-term survivors (4–6), but the effect of platinum-based chemotherapy has reached a plateau.

The failure pattern in patients with Stage III NSCLC treated by concurrent chemoradiotherapy was roughly local recurrence alone in one third of the patients, both local and distant recurrence in another third of patients, and distant metastasis without local failure in the remaining third of patients (2, 5).

Reprint requests to: Ikuo Sekine, M.D., Ph.D., Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. Tel : (+81) 3-3542-2511; Fax: (+81) 3-3542-3815; E-mail: isekine@ncc.go.jp

Presented at the 45th Annual Meeting of the American Society of Clinical Oncology, May 29—June 2, 2006, Orlando, Florida.

Supported in part by Ministry of Health, Labour and Welfare, Health and Labour Science Research Grants, Research on Clinical Trials' Infrastructure Development, H21-RINKEN (Kikan)-IP-PAN-005.

Conflict of interest: none.

Acknowledgment—The authors thank Asako Sakamoto for her work as data manager and Mika Nagai for manuscript preparation.

Received June 7, 2010, and in revised form Dec 27, 2010. Accepted for publication Jan 10, 2011.

Thus, improvement of local control and suppression of distant metastasis are essential for prolongation of patient survival.

The conventional total dose of thoracic radiotherapy in patients with inoperable NSCLC has been 60 Gy administered in 30 fractions. This dose was established in 1987 by randomized Radiation Therapy Oncology Group trials that demonstrated better 3-year survival with a radiation dose of 60 Gy than with lower doses (7). In these trials, two-dimensional treatment planning was used, wherein the tumor volume was defined on kilovoltage radiographs (7). Thereafter, the standard initial target volume included the primary tumor, metastatic lymph nodes, and adjacent uninvolved ipsilateral hilar and mediastinal regions (elective nodal irradiation: ENI). Except for selected patients, excessive toxicity hampered an increase of the total dose to over 60 Gy in patients with locally advanced NSCLC.

It is, however, time now to reconsider the optimal dose of thoracic radiotherapy using new techniques in patients with locally advanced NSCLC, for the following reasons. First, positron emission tomography (PET) provides more accurate diagnosis of mediastinal lymph node metastases (8) and more accurate quantification of the tumor volumes, especially when atelectasis is present (9). Second, three-dimensional conformal radiation therapy (3D-CRT) enables radiation oncologists to delineate the tumor and adjacent normal tissue more sharply and to choose beam angles to maximize tumor coverage with minimum irradiation of normal tissues (10). Third, omission of the ENI resulted in improvement of radiation-associated toxicity without worsening the local control rate of the tumor (11, 12). Thus, by use of these new techniques, the optimal dose of thoracic radiation could exceed the conventional 60 Gy.

Two dose escalation studies in patients with locally advanced NSCLC showed that the total dose of thoracic radiotherapy could be increased up to 90 Gy in concurrent chemoradiotherapy using the 3D-CRT technique combined with weekly carboplatin and paclitaxel chemotherapy (13, 14). In these trials, chemoradiotherapy was administered after induction chemotherapy. However, it remained unclear whether these doses could be delivered safely to the majority of patients with locally advanced NSCLC, because it is not known how many patients were screened for the trials and how many of them were actually registered, and because some of the registered patients were excluded from the chemoradiotherapy phase after induction chemotherapy. The total number of patients evaluated in the two trials was also limited. Furthermore, chemotherapy other than weekly carboplatin and paclitaxel has not been evaluated in the setting of combined chemotherapy with high-dose thoracic radiotherapy, to our knowledge. The objectives of the current study were (1) to evaluate the toxicity of concurrent high-dose 3D-CRT without ENI with cisplatin and vinorelbine for unresectable Stage III NSCLC, (2) to determine the maximum tolerated dose (MTD) of thoracic radiotherapy, and (3) to observe the antitumor effects of this regimen.

PATIENTS AND METHODS

Study design

This study was designed as a Phase I study at the National Cancer Center Hospital. The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center on July 28, 2005. We planned to treat 12 patients at a dose level and follow them up at least 6 months, and then escalate to the next level if 67% of the patients did not experience dose-limiting toxicity (DLT). We followed widely accepted normal tissue dose constraints. Patients with percent volume of the normal lung receiving 20 Gy or more (V_{20}) of greater than 30% were excluded and treated outside the study. Other dosimetric constraints were applied at the discretion of the treating radiation oncologist. Maximum doses exceeding 50 Gy to the spinal cord, 66 Gy to the esophagus, or 66 Gy to the brachial plexus were generally excluded.

Patient selection

Previously untreated patients with locally advanced NSCLC without effusion were screened for entry into this study. The eligibility criteria were (1) histologically or cytologically proven NSCLC, (2) unresectable Stage IIIA or IIIB disease confirmed by both computed tomography (CT) and PET, (3) no previous treatment, (4) measurable disease, (5) $V_{20} \leq 30\%$, (6) age ≥ 20 years, (7) Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, and (8) adequate bone marrow function (white blood cell [WBC] count $\geq 4.0 \times 10^9$/L, hemoglobin ≥ 9.5 g/dL, and platelet count $\geq 100 \times 10^9$/L), liver function (total bilirubin ≤ 1.5 mg/dL and transaminase ≤ 80 IU/L), renal function (serum creatinine ≤ 1.5 mg/dL), and pulmonary function ($PaO_2 \geq 70$ Torr under room air). Patients were excluded if (1) they had malignant pleural or pericardial effusion or (2) they had a concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified by a chest x-ray, infection, or other diseases contraindicating chemotherapy or radiotherapy, or (3) they were pregnant or breast feeding. All patients gave their written informed consent.

Pretreatment evaluation

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest x-rays, chest CT scan, brain CT scan or magnetic resonance imaging, abdominal CT, and PET.

Treatment schedule

Chemotherapy consisted of cisplatin 80 mg/m^2 on Day 1 and vinorelbine 20 mg/m^2 on Days 1 and 8, repeated every 4 weeks for three to four cycles. Cisplatin was administered by intravenous infusion for 60 minutes with 2,500 to 3,000 mL of intravenous fluid for hydration and prophylactic antiemetic therapy consisting of a 5-hydroxytriptamine-3 antagonist on Day 1 and a corticosteroid on Days 1 to 5. Vinorelbine, diluted in 50 mL of normal saline, was administered intravenously.

Radiation therapy started on Day 1 of the first cycle of chemotherapy and was delivered with megavoltage equipment (6–10 MV) once daily for 5 days a week. The total dose was 66 Gy in 33 fractions at level 1, 72 Gy in 36 fractions at level 2, and 78 Gy in 39 fractions at level 3. All patients underwent a 3D treatment planning CT 3 to 7 days before the start of the treatment, and the eligibility was finally confirmed based on evaluation using the

dose–volume histogram (DVH). The gross tumor volume (GTV) was defined as the primary tumor delineated on pulmonary windows of the chest CT or on the diagnostic PET scans. Atelectasis or secondary changes in the peripheral lung region of the primary tumor were not included. Metastatic lymph nodes defined as nodes of 1 cm or larger visualized on mediastinal windows of the CT images or PET-positive lymph nodes were also included in the GTV. The clinical target volume (CTV) was equivalent to the GTV. Uninvolved mediastinum or supraclavicular fossae were not included in the CTV. The planning target volume (PTV) was determined as the CTV plus 1.0 cm for the anterior, posterior, medial, and lateral margins and a 1.0 to 2.0 cm for the superior and inferior margins, taking account of setup variations and internal organ motion. The spinal cord dose was typically limited to 44 Gy, but a maximum of 50 Gy was allowed. The lung V_{20} was limited to 30% in all patients. The maximum dose to the brachial plexus and esophagus did not exceed 66 Gy. The 100% dose was prescribed to the reference point located in the central part of the PTV, and the entire PTV was covered with 95–107% of the prescribed dose principally, but variation of ±10% was allowed. Lung heterogeneity corrections using the equivalent path length algorithm were applied in all patients.

Toxicity assessment and treatment modification

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest x-ray were performed once a week during the course of treatment. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0). The lung toxicity grade was defined as the highest grade among cough, dyspnea, obstruction/stenosis of airways, pneumonitis/pulmonary infiltrates, and pulmonary fibrosis in the pulmonary/upper respiratory section (15).

Vinorelbine administration on Day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on Day 1: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, serum creatinine level ≥1.6 mg/dL, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. If these toxicities did not recover within 6 weeks from Day 1 of the previous cycle of chemotherapy, subsequent cycles of chemotherapy were stopped. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level rose to 2.0 mg/dL or higher. The dose of vinorelbine was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/L, platelet count $<25 \times 10^9$/L, or Grade 3 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: body temperature ≥38°C, Grade 3 esophagitis, PS of 3, or suspected radiation pneumonitis. Thoracic radiotherapy was terminated if any of the following were noted: Grade 4 esophagitis, Grade 3 or 4 pneumonitis, PS of 4, or duration of radiotherapy of over 62 days (level 1), 67 days (level 2), or 70 days (level 3). Any protocol-defined treatments were terminated if Grade 4 nonhematologic toxicities other than transient electrolyte disturbances or a PS of 4 was noted.

Dose-limiting toxicity and maximum tolerated dose

The DLT was defined as the following toxicities observed during a 6-month period from the start of treatment: (1) Grade 3 esophagitis, lung toxicity, myelitis, dermatitis associated with radiation, and cardiac toxicity associated with radiation, (2) Grade 4 nonhematologic toxicity, or (3) treatment termination due to prolonged toxicity. Twelve patients were enrolled at each dose level. All patients were followed up for at least 6 months to evaluate DLT. During the period, if none to 4 of the 12 patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If 5 or more of the 12 patients experienced DLT, that level was considered to be the MTD. The recommended dose for Phase II trials was defined as the dose preceding the MTD.

Response evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0 (16).

Follow-up

Patients who completed the protocol therapy were followed up to monitor toxicity, response, and recurrence. CT of the chest was performed every 2 to 4 months for 1 year, every 6 months for 2 years, and then yearly for 2 years. The relapse pattern was categorized into (1) local alone, including relapse from the primary site or the hilar, mediastinal, or supraclavicular lymph nodes, (2) distant metastasis alone, including pleural dissemination, pleural and pericardial effusions, and distant metastases, and (3) local and distant.

Statistical analyses

Progression-free survival time (PFS) and OS were estimated by the Kaplan-Meier method. The PFS was measured from the date of registration to the date of disease progression or death resulting from any cause or date of last follow-up. The OS was measured from the date of registration to the date of death resulting from any cause or date of last follow-up. Patients who were lost to follow-up without events were censored at the date of their last known follow-up. A confidence interval (CI) for the response rate was calculated by the method used for exact binomial CIs. The Dr. SPSS II 11.0 software package for Windows (SPSS Japan Inc., Tokyo, Japan) was used for the statistical analyses.

RESULTS

Registration and characteristics of the patients

From August 2005 to September 2008, 57 patients were deemed to initially be eligible. Of these, 3 patients were excluded because idiopathic interstitial pneumonitis (n = 1) and anemia (n = 2) developed. Explanation of the study using the consent form was given to 54 patients, and informed consent was obtained in 51 patients. The 51 patients underwent 3D treatment planning, and eligibility was finally confirmed in 31 patients. Those 31 were enrolled into this study. A total of 20 patients were excluded as a result of the DVH evaluation: because of V_{20} higher than 30% in 10 patients, overdose to the esophagus in 8 patients, and overdose to the brachial plexus in 2 patients. Eventually, of 17 patients assessed as to their eligibility for dose level 1, 16 patients for dose level 2, and 24 patients to dose level 3, 13 (76%), 12 (75%), and 6 (25%) patients were actually enrolled into levels 1 to 3, respectively (Fig. 1).

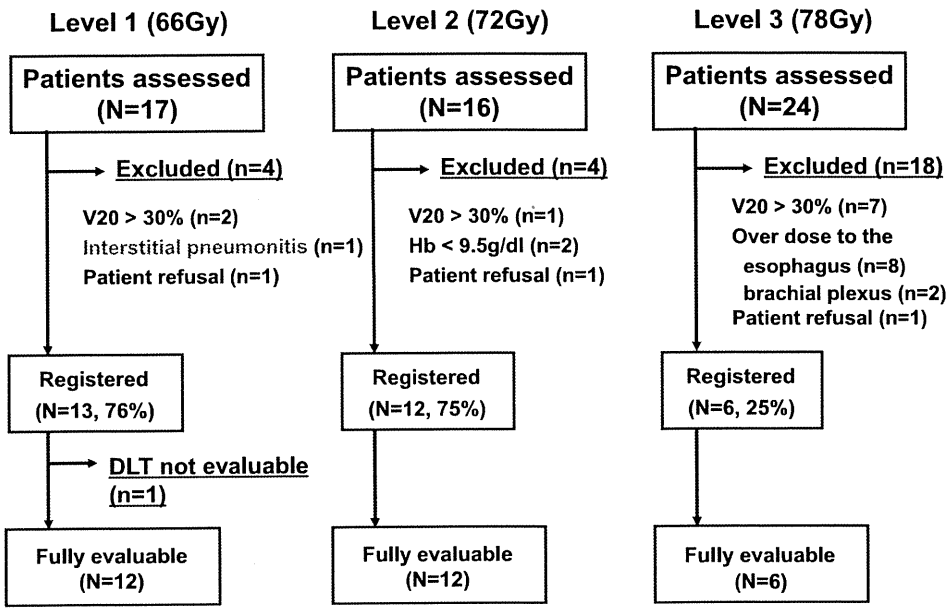

Fig. 1. Algorithm illustrating the flow of the patients. Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were actually enrolled at dose levels 1, 2, and 3, respectively.

The pretreatment characteristics of the patients enrolled in this trial are shown in Table 1. The majority of the patients were in good general condition, with a PS of 0 in 25 (81%) and no weight loss in 26 (84%) patients. Adenocarcinoma was the predominantly encountered histological characteristic, seen in 23 (74%) patients.

Treatment delivery

The treatment delivery to the patients was fairly good (Table 2). The planned dose of radiotherapy was administered to all patients of all the three dose levels. More than 80% of the patients received three to four cycles of chemotherapy without or with only one omission of vinorelbine on Day 8, regardless of the dose levels.

Toxicity and DLTs

The hematologic toxicity was comparable to that of other concurrent chemoradiotherapy (Table 3). Grade 4 septic shock was encountered during the fourth cycle of chemotherapy in 1 patient enrolled at dose level 1, but it was manageable by standard care with antibiotics. Other nonhematologic toxicities were mild and acceptable.

Table 1. Patient characteristics

Characteristic	*n*	(%)
Sex		
M	26	(84)
F	5	(16)
Age (y)		
Median (range)	60	(41–75)
Performance status		
0	25	(81)
1	6	(19)
Body weight loss (%)		
0	26	(84)
0.1–5.0	2	(6)
≤5.0	3	(10)
Histology		
Adenocarcinoma	23	(74)
Squamous cell carcinoma	4	(13)
NSCLC, not otherwise specified	4	(13)
Stage		
IIIA	20	(65)
IIIB	11	(35)

Abbreviation: NSCLC = non–small-cell lung cancer.

Table 2. Treatment delivery

	Level 1 (*n* = 13)	Level 2 (*n* = 12)	Level 3 (*n* = 6)
Radiotherapy			
Total dose (Gy)			
66	13 (100)	–	–
72	–	12 (100)	–
78	–	–	6 (100)
Delay (days)			
≤5	11 (85)	5 (42)	5 (83)
6–10	2 (15)	6 (50)	0
11–15	0	1 (8)	1 (17)
Chemotherapy			
No. of cycles			
4	6 (46)	6 (50)	4 (67)
3	6 (46)	4 (33)	2 (33)
2	0	1 (8)	0
1	1 (8)	1 (8)	0
No. of VNR omissions			
0	10 (77)	7 (58)	2 (33)
1	2 (15)	4 (33)	3 (50)
2	0	0	1 (17)
3	1 (8)	1 (8)	0

Abbreviation: VNR = vinorelbine administered on Day 8.

Table 3. Toxicity

	Grade										
	Level 1			(n = 13)	Level 2			(n = 12)	Level 3			(n = 6)
Toxicity	2	3	4	(3+4 %)	2	3	4	(3+4 %)	2	3	4	(3+4 %)
Leukopenia	4	6	2	(62)	1	3	8	(92)	1	3	2	(83)
Neutropenia	4	4	4	(62)	0	1	10	(92)	1	3	2	(83)
Anemia	8	2	2	(31)	7	3	1	(33)	2	2	0	(50)
Thrombocytopenia	0	0	0	(0)	1	1	0	(8)	0	0	0	(0)
Febrile neutropenia	–	1	0	(8)	–	3	0	(25)	–	1	0	(17)
Infection	0	0	1	(8)	0	1	0	(8)	2	0	0	(0)
Esophagitis	1	1	0	(8)	2	1	0	(8)	0	0	0	(0)
Lung toxicity	2	0	0	(0)	0	0	0	(0)	0	1	0	(17)
Anorexia	3	0	0	(0)	2	2	0	(17)	0	0	0	(0)
Nausea	3	0	0	(0)	3	0	0	(0)	0	0	0	(0)
ALT elevation	1	1	0	(8)	0	0	0	(0)	1	0	0	(0)
CRN elevation	7	0	0	(0)	4	0	0	(0)	0	0	0	(0)

Abbreviations: ALT = alanine aminotransferase; CRN = creatinine.

Of the 13 patients at dose level 1, one was excluded from the analysis of the DLT because he received only one cycle of chemotherapy as a result of the development of cisplatin-induced renal toxicity. Two (17%) of the remaining 12 patients at this dose level developed DLT: Grade 3 esophagitis in 1 patient and Grade 4 septic shock in the other. At dose level 2, two (17%) DLTs were noted: Grade 3 esophagitis in 1 patient and treatment delay by more than 15 days in the other. One (17%) of the 6 patients at dose level 3 developed Grade 3 bronchial stenosis without local recurrence of the disease. This was considered to be a Grade 3 lung toxicity and was counted as DLT. No other DLTs were noted. Thus, inasmuch as the incidence of DLT was below 33% at all dose levels, MTD was not reached.

Preliminary efficacy results

Objective responses and survival were evaluated in the 31 patients. Two patients showed complete responses and 27 showed partial responses, which represented a response rate (95% CI) of 94% (79–99). Disease progression was noted in 23 patients, and the median PFS was 11.6 months with a median duration of follow-up of 30.5 (range, 9.0–49.5) (Fig. 2). The first relapse sites aresummarized in Table 4. Brain metastasis alone as the first relapse site was noted in 7 (23%) patients. The median OS was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively (Fig. 3).

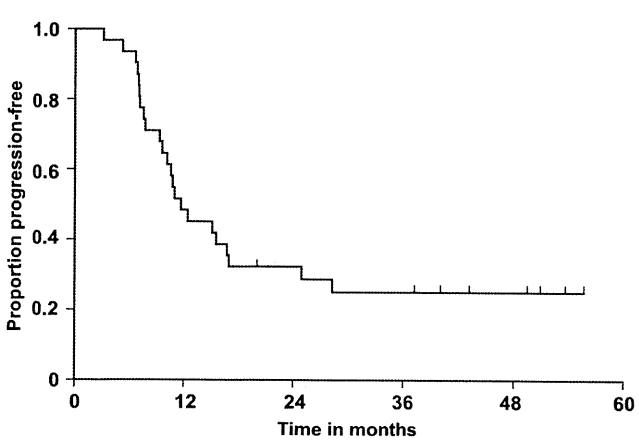

Fig. 2. Progression-free survival (n = 31). The median progression-free survival was 11.6 months, with a median duration of follow-up of 30.5 months (range, 9.0–49.5 months).

DISCUSSION

This study showed that concurrent 3D-CRT to the thorax with cisplatin plus vinorelbine chemotherapy was safe even up to 78 Gy in patients with unresectable Stage III NSCLC. This does not mean, however, that doses as high as 78 Gy can be given to all patients with this disease, because the safety in this study was shown only in highly selected patients by a PET/CT and DVH evaluation and by the standard staging procedure. Twenty-five of the 33 patients met the eligibility criteria for enrollment at dose levels 1 and 2, whereas only 6 of the 24 patients could be enrolled at dose level 3 in this study—that is, only one fourth of the patients could be treated with 78 Gy. Thus, this study showed that 72 Gy was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints, which forced three quarters of the enrolled patients at the 78-Gy level to not

Table 4. First relapse sites (n = 31)

Sites	n	(%)
Local recurrence alone	6	(19)
Local and distant metastasis	6	(19)
Distant metastasis alone	11	(35)
Brain alone	7	(23)
No relapse	8	(26)

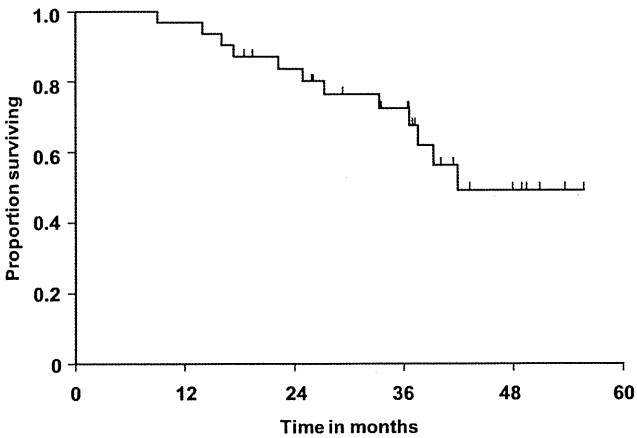

Fig. 3. The median overall survival was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively.

be eligible on the basis of those normal tissue constraints, and that the maximum tolerated dose was not determined because of this issue.

One obstacle to enrolling patients at dose level 3 was that the lung V_{20} often exceeded 30% when the total dose was increased to 78 Gy. This lung V_{20} dose constraint might have been too strict. According to a recent review, it is prudent to limit V_{20} to ≤30–35% with conventional fractionation, but there is no sharp dose threshold below which there is no risk for severe radiation pneumonitis (17). This is partly because DVH-based parameters will change at specific phases of the respiratory cycle when CT images for DVH evaluation have been obtained, there is uncertainty regarding how much of the bronchus should be defined as lung, and the lung edges may vary with the CT window level setting. In addition, patient-associated factors such as age, smoking status, lung function, and preexisting lung damage may influence the incidence and severity of radiation pneumonitis (18). If the threshold of V_{20} were set at higher than 30% (*e.g.*, 35%), then more patients would meet the eligibility criteria, but safety might not be guaranteed. Given that the definite threshold cannot be determined, a strict constraint should be introduced. This study showed that the lung toxicity was acceptable when the V_{20} was kept within 30%; therefore, we decided to use this eligibility criterion for concurrent chemotherapy and high-dose radiotherapy for a subsequent Phase II study.

Another obstacle was overdose to the esophagus and brachial plexus, which were close to the subcarinal (No. 7) and supraclavicular lymph nodes, respectively, that were frequently involved in patients with advanced NSCLC; therefore, the volume of these serial organs were included, in part, in the PTV in many patients with Stage III disease. The radiation tolerance doses of these organs have been defined as no higher than 72 Gy when one third of the organs are included in the irradiation volume (19). However, few data are available on the radiation tolerance doses of normal organs in humans; therefore, whether or not radiation doses above 72 Gy may be tolerated is unknown, especially when only small percentages of the organs are actually included in the irradiation volume. Notwithstanding, we do not agree that the radiation dose can be increased close to the intolerable level, because serious radiation toxicity to these serial organs could be irreversible, frequently leaves severe sequelae, and is fatal in some cases.

The toxicity observed in this trial was comparable to that in our previous study of concurrent chemoradiotherapy with vinorelbine and cisplatin chemotherapy plus thoracic radiation at a total dose of 60 Gy administered in 30 fractions: Grade 3–4 neutropenia in 77% and 67% of patients, Grade 3–4 esophagitis in 6% and 12% of patients, and Grade 3–5 lung toxicity in 3% and 7% in the current and previous studies, respectively (5). This suggests that patient selection using PET/CT and DVH evaluation may be useful to keep the toxicity associated with high-dose thoracic radiation within the range of toxicity induced by conventional-dose thoracic radiation.

In this study, a remarkably high proportion (74%) of subjects had adenocarcinoma, which may provide an explanation for the high rate of subsequent brain metastases. Patient selection also affects the treatment efficacy considerably; therefore, it is difficult to compare it between the current and previous studies. However, the median PFS of 11.6 months and median OS of 41.9 months sound promising. We are conducting a Phase II study of concurrent 3D-CRT at a total dose of 72 Gy and chemotherapy with cisplatin and vinorelbine.

In conclusion, concurrent 3D-CRT with cisplatin and vinorelbine chemotherapy was feasible up to 72 Gy, in patients with unresectable Stage III NSCLC. At the level of 78 Gy, however, only 25% of the patients assessed for eligibility were found to be actually eligible. Thus, 72 Gy in 36 fractions was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints when administered concurrently with cisplatin and vinorelbine.

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Randomized Phase II Study of Carboplatin-Paclitaxel or Gemcitabine-Vinorelbine in Patients With Advanced Nonsmall Cell Lung Cancer and a Performance Status of 2

West Japan Thoracic Oncology Group 0004

Hiroshi Saito, MD, PhD, Kazuhiko Nakagawa, MD, PhD,† Koji Takeda, MD,‡ Yasuo Iwamoto, MD, PhD,§ Masahiko Ando, MD, PhD,‖ Masao Maeda, MD,* Nobuyuki Katakami, MD, PhD,¶ Takashi Nakano, MD, PhD,# Takayasu Kurata, MD, PhD, ** and Masahiro Fukuoka, MD, PhD†*

Objectives: The aim of the present study was to evaluate the efficacy and safety of carboplatin plus paclitaxel versus gemcitabine plus vinorelbine in patients with advanced nonsmall cell lung cancer (NSCLC) and an Eastern Cooperative Oncology Group performance status (PS) of 2.

Methods: Chemotherapy-naive patients with NSCLC of stage IIIB or IV and a PS of 2 were eligible. The patients received 3-week cycles of carboplatin (area under the curve of 6) plus paclitaxel (200 mg/m^2) on day 1 (CP) or gemcitabine (1000 mg/m^2) plus vinorelbine (25 mg/m^2) on days 1 and 8 (GV). The primary end point was 1-year survival rate for selection of the better treatment arm for further study.

Results: Of the 89 patients enrolled, 84 were assessable (41 in the CP arm, 43 in the GV arm). The overall response rate, median survival time, and 1-year survival rate were 29.3%, 5.9 months, and 22.0%, respectively, for the CP arm and 20.9%, 6.0 months, and 27.9% for the GV arm. Common toxicities of grade 3 or 4 included neutropenia (67.5% for the CP arm vs. 65.1% for the GV arm), febrile neutropenia (20% vs. 14%), and infection (25.0% vs. 23.2%). The frequency of nausea of grade 3 was greater for the CP arm (17.5% vs. 2.3%), whereas that of anemia of grade 3 or 4 (30.2% vs. 12.5%) or treatment-related death (7.0% vs. 2.4%) was greater for the GV arm.

Conclusions: The 1-year survival rate did not exceed 30% for either doublet chemotherapy. Furthermore, each treatment was associated with a substantial degree of toxicity.

Key Words: carboplatin, paclitaxel, gemcitabine, vinorelbine, nonsmall cell lung cancer, performance status

(*Am J Clin Oncol* 2012;35:58–63)

From the *Department of Respiratory Medicine, Aichi Cancer Center Aichi Hospital, Okazaki; †Department of Medical Oncology, Kinki University Hospital, Osakasayama; ‡Department of Clinical Oncology, Osaka City General Hospital, Osaka; §Department of Medical Oncology, Hiroshima City General Hospital, Hiroshima; ‖Health Service, Kyoto University, Kyoto; ¶Department of Respiratory Medicine, Kobe City General Hospital, Kobe; #Department of Respiratory Medicine, Hyogo College of Medicine, Nishinomiya; and **Cancer Chemotherapy Center, Osaka Medical College, Takatsuki, Japan.

Masahiro Fukuoka has received honoraria from AstraZeneca, Chugai, and Boehringer Ingelheim. The other authors declare no conflicts of interest.

Reprints: Hiroshi Saito, MD, PhD, Department of Respiratory Medicine, Aichi Cancer Center Aichi Hospital, 18 Kuriyado Kake-machi, Okazaki 444-0011, Japan. E-mail: hsaito@acc-aichi.com.

ISSN: 0277-3732/12/3501-0058
DOI: 10.1097/COC.0b013e318201a0f3

Nonsmall cell lung cancer (NSCLC) accounts for nearly 85% of all cases of lung cancer, with most affected individuals presenting with inoperable advanced disease. Meta-analyses have shown that cisplatin-based chemotherapy results in a moderate improvement in the survival of patients with advanced NSCLC.[1–3] Such chemotherapy has thus become the standard treatment for patients with this condition.

The development of third-generation agents including vinorelbine, gemcitabine, taxanes, and irinotecan has resulted in their incorporation into various chemotherapy regimens for evaluation in randomized controlled studies.[4–8] However, it has not been possible to generalize treatment approaches based on the results of these studies to all patients with advanced NSCLC, in particular to those with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2, given that such individuals have frequently been excluded from the studies.[4–8] Optimal chemotherapy for patients with advanced NSCLC and a PS of 2 thus remains to be established, despite the fact that individuals with a PS of 2 account for up to 30% to 40% of all patients with lung cancer according to population-based surveys.[9,10] Investigations of chemotherapeutic regimens specifically in this patient population are therefore warranted.

Chemotherapy options include monotherapy with a third-generation agent and either platinum-based or nonplatinum-based combination chemotherapy with a third-generation agent. Although monotherapy with third-generation agents has been compared with best supportive care, with some of the agents having been found to confer a survival advantage in patients with advanced NSCLC,[11–14] most of the studied patients had a PS of 0 or 1 and the 1-year survival rates (with the exception of that for vinorelbine in elderly individuals) did not exceed 30%. To select a promising experimental arm of combination chemotherapy with third-generation agents for further phase III study in patients with advanced NSCLC and a PS of 2, for whom monotherapy is a standard treatment, we have therefore now performed a randomized phase II study comparing the platinum-based doublet combination of carboplatin plus paclitaxel (CP) with the nonplatinum-based doublet combination of gemcitabine plus vinorelbine (GV).

PATIENTS AND METHODS

Eligibility Criteria

Chemotherapy-naive patients with a PS of 2 and a cytologically or histologically proven diagnosis of NSCLC

were eligible for the study. Other eligibility criteria included a disease stage of IIIB with malignant effusion or stage IV, or relapse after surgery or radiotherapy; measurable or evaluable disease; a life expectancy of ≥ 3 months; no concomitant malignancy; an age of >18 years; and adequate baseline organ function defined as a neutrophil count of $\geq 1500/mm^3$, platelet count of $\geq 100,000/mm^3$, serum total bilirubin of ≤ 1.5 mg/dL, serum aspartate aminotransferase and alanine aminotransferase of ≤ 5 times the upper limit of the normal range (ULN), serum creatinine of ≤ 1.5 mg/dL, and a 24-hour creatinine clearance rate of ≥ 60 mL/min. Patients with brain metastases were eligible if they had been treated with surgery or radiotherapy and were stable. Individuals were ineligible if they had active and serious infections, massive pleural or pericardial effusion that required drainage, concomitant serious cardiovascular disease, or neuropathy of grade 2 or higher, or if they were pregnant or lactating. The study protocol was approved by the review board of each institution, and all patients provided written informed consent before enrollment.

Randomization

Eligible patients were randomly assigned to 1 of the 2 treatment arms by a minimization method with disease stage (IIIB vs. IV) and body weight loss in the previous 6 months (<5% vs. $\geq 5\%$) as stratifying variables. Randomization was performed at the West Japan Thoracic Oncology Group (now known as the West Japan Oncology Group) Data Center.

Treatment Schedule

Treatment with CP or GV was repeated every 3 weeks for up to 6 cycles unless there was evidence of disease progression, unacceptable toxicity, or withdrawal of consent. Continuation of the chemotherapy beyond 6 cycles was permitted at the discretion of the treating physician. In the CP arm, patients were treated intravenously with paclitaxel (200 mg/m^2) on day 1 and carboplatin (area under the curve of 6 mg/mL × min) on day 1. Paclitaxel was infused over 3 hours, after administration of dexamethasone, diphenhydramine, and ranitidine; carboplatin was administered over 60 minutes. In the GV arm, patients were treated intravenously with vinorelbine (25 mg/m^2) and gemcitabine (1000 mg/m^2) on days 1 and 8. Vinorelbine was administered over 6 to 10 minutes, and gemcitabine over 30 minutes. Gemcitabine and vinorelbine were withheld on day 8 if a patient had a leukocyte count of $<2000/mm^3$ or a platelet count of $<70,000/mm^3$ or manifested a nonhematologic toxicity (excluding nausea, vomiting, or alopecia) of grade 2 or higher.

Dose Modification

Dose modification was performed in response to any toxicity that occurred. If there was development of febrile neutropenia or in the event of a platelet nadir count of $<25,000/mm^3$ or thrombocytopenia requiring a platelet transfusion, then the dose of both drugs was reduced by 25% in the subsequent cycle in both arms. In the event of nausea, vomiting, or mucositis, each of grade 3 or higher, the dose of both the agents was reduced by 20% in the subsequent cycle in both arms. If hepatic toxicity (defined as a serum total bilirubin concentration of ≥ 1.5 times ULN or serum aspartate aminotransferase or alanine aminotransferase of >5 times ULN) was detected on the treatment day, the dose of paclitaxel was reduced by 25% in the CP arm, whereas the dose of both gemcitabine and vinorelbine was reduced by 25% in the GV arm. The dose of both paclitaxel and vinorelbine was reduced by 20% or 30% in the event of neurotoxicity of grade 2 or 3, respectively. If other types of toxicity of grade 3 or higher were observed, the dose of all agents was reduced by 50% in the subsequent cycle. Prophylactic use of granulocyte colony-stimulating factor was not permitted.

Study Evaluations

The pretreatment baseline evaluation included a complete medical history and physical examination, complete blood cell count, blood chemistry, urinalysis, chest radiography, computed tomography (CT) of the chest, CT or ultrasound examination of the abdomen, CT or magnetic resonance imaging of the brain, bone scintigraphy, arterial blood gas analysis, and electrocardiography. Complete blood cell count, blood chemistry, and urinalysis were repeated weekly. CT of the chest was planned to be repeated every 4 weeks for response evaluation. All of these assessments were planned to be repeated at the end of the study unless the patient had progressive disease. The World Health Organization criteria were used for response assessment.[15] Toxicity was evaluated according to the National Cancer Institute-Common Toxicity Criteria version 2.0.

Symptom Assessment

Disease-related symptoms were assessed according to the Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung quality of life instrument (version 4.0).[16] The patients were asked to complete the instrument at the time of enrollment as well as at 3 and 6 weeks after the initiation of treatment. The maximum attainable score on the LCS was 28, in which case the patient was considered to be asymptomatic. An increase of 2 or more points from the baseline score was defined as clinically meaningful symptom improvement.

Statistical Analysis

The primary end point of the study was the 1-year survival rate, and the secondary end points included response rate, time to progression, symptom improvement, and toxicity. The sample size was calculated on the basis of the randomized phase II study selection design of Simon et al.[17] In ECOG 1594, which evaluated 4 platinum doublets in patients with advanced NSCLC, the 1-year survival rate in patients with a PS of 2 was 19.1%.[18] On the basis of this result, we assumed 20% as a baseline 1-year survival rate. The study was therefore designed to select the better treatment with 85% probability if the expected baseline 1-year survival rate was 20% and the absolute difference in 1-year survival rate was at least 10%. A total of 41 evaluable patients were thus required in each arm of the study. We chose a sample size of 90 patients in total, assuming a 10% dropout rate. The treatment feasibility of both arms was separately evaluated in a 2-stage design, with treatment-related death or toxicity of grade 4 (excluding uncomplicated hematologic toxicity) as a surrogate for feasibility. In the first stage, if 2 or more treatment-related deaths or 9 or more cases of grade 4 toxicity were observed per 20 patients, the treatment would be considered unacceptable and the study would be terminated. In the second stage, if 3 or more treatment-related deaths or 24 or more incidences of grade 4 toxicity were observed per 45 patients, then the treatment would be considered unfeasible.

The duration of treatment response and survival was measured from the day of registration, and the overall survival curve and progression-free survival curve were calculated by the method of Kaplan and Meier.[19] The frequencies of toxicities were compared between the 2 arms with the use of

the χ^2 test. For symptom analysis, LCS values were compared between the study arms with linear mixed-effects models (in which the missing data depended on the observed LCS) with the use of the MIXED procedure in SAS version 9 software (SAS Institute, Cary, NC). All comparisons were 2-sided, and a P value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Between May 2001 and August 2005, 89 patients were enrolled in the study, with 44 individuals being randomly assigned to CP and 45 to GV. Two patients were subsequently considered to be ineligible and 3 did not receive the protocol treatment. A total of 84 patients (41 in the CP arm and 43 in the GV arm) were therefore assessable for an intention-to-treat analysis. The baseline demographics of the 84 patients are listed in Table 1. Although the frequency of comorbidity was higher in the GV arm than in the CP arm, the difference was not statistically significant ($P=0.14$). The other demographic parameters also did not differ significantly between the 2 arms.

Treatment Administration

Patients in the CP arm received a median of 2 treatment cycles (range, 1-8), compared with a median of 3 cycles (range, 1-12) in the GV arm. The percentage of the planned dose was 92.1% each for carboplatin and paclitaxel, 88.8% for gemcitabine, and 88.7% for vinorelbine. The reasons for discontinuation of treatment included progressive disease (41.5% for CP vs. 37.2% for GV, $P=0.69$), patient refusal (22% vs. 14%, $P=0.34$), toxicity including treatment-related death (12.2% vs. 23.2%, $P=0.19$), and others (4.9% vs. 11.6%, $P=0.26$).

TABLE 1. Patient Characteristics

Characteristic	CP (N = 41)	GV (N = 43)
Age (y)		
Median	65	67
Range	20-77	34-76
Sex		
Male	30 (73.2)	31 (72.1)
Female	11 (26.8)	12 (27.9)
Histologic type		
Adenocarcinoma	27 (65.9)	32 (74.4)
Squamous cell	13 (31.7)	8 (18.6)
Other	1 (2.4)	3 (7)
Stage		
IIIB	7 (17.1)	7 (16.3)
IV	34 (82.9)	36 (83.7)
Body weight loss		
<5%	17 (41.5)	19 (44.2)
≥5%	24 (58.5)	24 (55.8)
Earlier treatment		
None	35 (85.4)	32 (74.4)
Surgery	3 (7.3)	4 (9.3)
Radiotherapy	3 (7.3)	6 (14)
Other	0 (0)	1 (2.3)
Smoking history		
Yes	32 (78)	33 (76.7)
No	9 (22)	10 (23.3)
No. comorbidities		
None	30 (73.2)	26 (60.5)
One	10 (24.4)	11 (25.6)
Two	1 (2.4)	6 (14)

Values in parentheses are percentages.
CP indicates carboplatin plus paclitaxel; GV, gemcitabine plus vinorelbine.

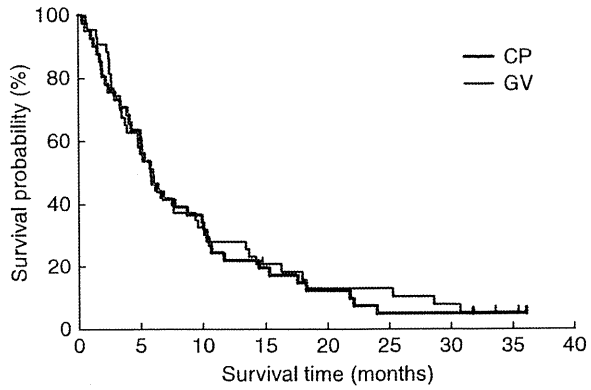

FIGURE 1. Overall survival curves according to treatment arm. CP indicates carboplatin-paclitaxel; GV, gemcitabine-vinorelbine.

Response and Survival

In the CP arm, one patient achieved a complete response and 11 patients showed a partial response, with an overall response rate of 29.3% [95% confidence interval (CI), 16.1%-45.5%]. In the GV arm, 9 patients showed a partial response, with an overall response rate of 20.9% (95% CI, 10.0%-36.0%). At the time of analysis (October 2, 2006), the median follow-up time was 5.8 months (range, 0.3-36.1 mo) and 2 patients (4.9%) in the CP arm and 3 patients (7.0%) in the GV arm remained alive. The 1-year survival rate was 22.0% (95% CI, 9.3%-34.6%) for CP and 27.9% (95% CI, 14.5%-41.3%) for GV. The median survival time (Fig. 1) and time to progression (Fig. 2) were 5.9 and 2.9 months, respectively, for CP, and 6.0 and 2.7 months for GV.

Toxicity

In the CP arm, 1 patient did not complete the first cycle of treatment because of the development of hypersensitivity during paclitaxel administration. Toxicity was therefore assessable in a total of 83 patients. The major toxicities observed are listed in Tables 2 and 3. The frequency of neutropenia of grade 3 or 4 was similar in the CP and GV arms (67.5% vs. 65.1%, respectively), as was that of febrile neutropenia of grade 3 or 4

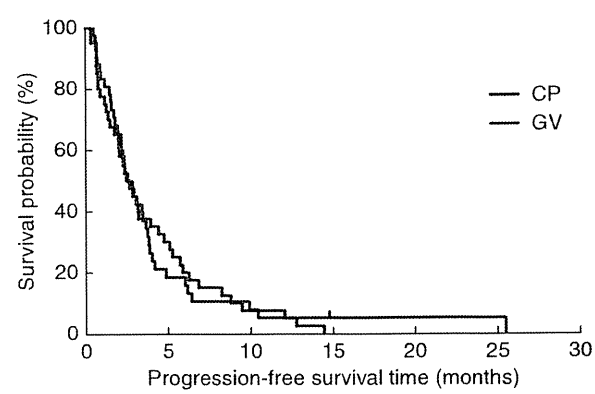

FIGURE 2. Progression-free survival curves according to treatment arm. CP indicates carboplatin-paclitaxel; GV, gemcitabine-vinorelbine.

TABLE 2. Hematologic Toxicities

Toxicity	CP (N = 40)	GV (N = 43)	*P*
Leukopenia			0.09
Grade 3	11 (27.5)	16 (37.2)	
Grade 4	3 (7.5)	7 (16.3)	
Neutropenia			0.82
Grade 3	14 (35)	13 (30.2)	
Grade 4	13 (32.5)	15 (34.9)	
Anemia			0.05
Grade 3	3 (7.5)	11 (25.6)	
Grade 4	2 (5)	2 (4.7)	
Thrombocytopenia			0.52
Grade 3	3 (7.5)	5 (11.6)	
Grade 4	0 (0)	0 (0)	
Febrile neutropenia			0.46
Grade 3	8 (20)	6 (14)	
Grade 4	0 (0)	0 (0)	

Values in parentheses are percentages.
CP indicates carboplatin plus paclitaxel; GV, gemcitabine plus vinorelbine.

(20% vs. 14%). The prevalence of infection of grade 3 or 4 exceeded 20% in both arms, but most such infections were of grade 3 and were clinically manageable. The frequency of anemia of grade 3 or 4 was higher in the GV arm (30.2% vs. 12.5%), with this difference being of borderline significance ($P = 0.05$). Nausea of grade 3 occurred more frequently in the CP arm ($P = 0.019$), but no patient in either arm developed nausea of grade 4. There were 4 treatment-related deaths, 1 (2.4%) in the CP arm and 3 (7.0%) in the GV arm. The treatment-related death in the CP arm was attributable to pneumonia. In the GV arm, the first patient died from pneumonia 30 days after the onset of the first cycle of treatment; the second patient died at home on day 19 of the third cycle, with a neutrophil count on day 15 of 190/mm^3; and the third patient fell into a state of shock several hours after receiving the first cycle of chemotherapy and died on the same day.

TABLE 3. Nonhematologic Toxicities

Toxicity	CP (N = 40)	GV (N = 43)	*P*
Nausea			0.019
Grade 3	7 (17.5)	1 (2.3)	
Grade 4	0 (0)	0 (0)	
Vomiting			0.30
Grade 3	1 (2.5)	0 (0)	
Grade 4	0 (0)	0 (0)	
Diarrhea			0.96
Grade 3	1 (2.5)	1 (2.3)	
Grade 4	0 (0)	0 (0)	
Infection			0.85
Grade 3	8 (20)	9 (20.9)	
Grade 4	2 (5)	1 (2.3)	
AST or ALT			0.19
Grade 3	1 (2.5)	3 (7)	
Grade 4	0 (0)	1 (2.3)	
Pneumonitis			0.71
Grade 3	1 (2.5)	2 (4.7)	
Grade 4	1 (2.5)	1 (2.3)	
Sensory neuropathy			0.14
Grade 3	2 (5)	0 (0)	
Grade 4	0 (0)	0 (0)	

Values in parentheses are percentages.
ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CP, carboplatin plus paclitaxel; GV, gemcitabine plus vinorelbine.

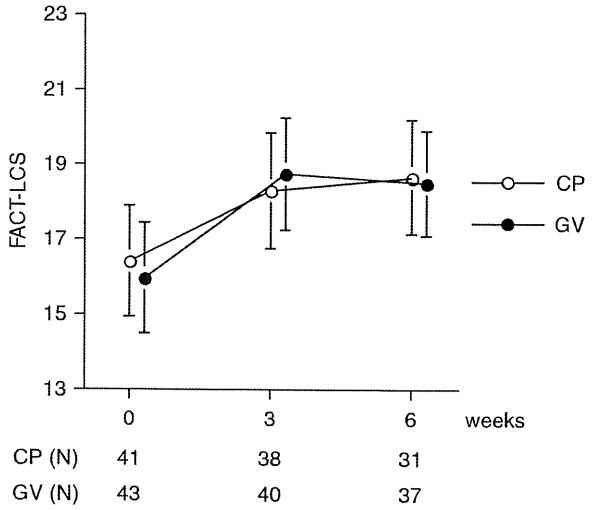

FIGURE 3. Symptom assessment based on the Lung Cancer Subscale of the Functional Assessment of Cancer Therapy-Lung instrument (FACT-LCS) and according to treatment arm. CP indicates carboplatin-paclitaxel; GV, gemcitabine-vinorelbine. Data are least squares ± SEM.

Symptom Improvement

All 84 patients filled in the baseline LCS questionnaire; the questionnaire completion rate was 92.9% at 3 weeks and 81.0% at 6 weeks (Fig. 3). The adjusted means of the initial summed scores of the LCS were 16.4 for CP and 16.0 for GV. The summed scores had improved at 3 and 6 weeks after treatment onset ($P = 0.01$ in both arms). However, no statistically significant difference was observed between the 2 arms ($P = 0.85$). At 3 weeks, an improvement in the summed scores (increase of 2 or more from the baseline score) was observed in 46.3% of patients in the CP arm and in 55.8% of those in the GV arm; at 6 weeks, the values were 41.5% for CP and 44.2% for GV.

Second-line Treatment

The percentages of patients who underwent second-line chemotherapy were similar in the 2 arms (39% for CP vs. 37% for GV). Gefitinib was administered to 7 patients in the CP arm and to 6 in the GV arm, whereas docetaxel was administered to 6 patients in each of the 2 arms.

DISCUSSION

We have evaluated platinum-based and nonplatinum-based doublet chemotherapy in patients with advanced NSCLC and a PS of 2 and found that the 1-year survival rate did not exceed 30% in either of the treatment arm (22.0% vs. 27.9%, respectively), with median survival times of nearly 6 months (5.9 vs. 6.0 mo, respectively) and a median time to progression of approximately 3 months. A randomized phase II study (ECOG 1599) previously compared CP with cisplatin plus gemcitabine in patients with advanced NSCLC and a PS of 2 and found that the median survival time, time to progression, and 1-year survival rate were 6.2 months, 4.2 months, and 19%, respectively, for CP and 6.9 months, 4.8 months, and 25% for cisplatin plus gemcitabine.[20] Our present results for median survival time and 1-year survival rate are thus similar

to those of ECOG 1599. However, the time to progression was shorter in our study than in ECOG 1599, with this difference possibly being attributable to the fact that CT of the chest was repeated every 4 weeks in the present study.

An unresolved issue regarding optimal chemotherapy for patients with advanced NSCLC and a PS of 2 concerns the relative merits of single-agent versus doublet chemotherapy. The Cancer and Leukemia Group B performed a randomized phase III study comparing paclitaxel alone versus CP in patients with advanced NSCLC.[21] Subset analysis focusing on 99 patients with a PS of 2 revealed a better survival outcome with CP than with paclitaxel alone; the median survival time and 1-year survival rate were 4.7 months and 18%, respectively, for the combination therapy and 2.4 months and 10% for the monotherapy. In contrast, the Hellenic Cooperative Oncology Group conducted a randomized phase II study comparing gemcitabine alone with carboplatin plus gemcitabine in patients with advanced NSCLC and a PS of 2 and found no difference in survival outcome between the 2 arms of the study[22]; the median survival time and 1-year survival rate were 4.8 months and 17.8%, respectively, for gemcitabine alone and 6.7 months and 20% for carboplatin plus gemcitabine. A randomized phase III study comparing weekly docetaxel with docetaxel plus gemcitabine in elderly or PS 2 patients with advanced NSCLC revealed no difference in overall survival between the 2 arms for the patients with a PS of 2, with median survival times of 2.9 months for docetaxel versus 3.8 months for docetaxel plus gemcitabine.[23]

More recently, 2 randomized phase III studies dedicated to patients with advanced NSCLC and a PS of 2 compared either paclitaxel poliglumex in combination with carboplatin versus paclitaxel plus carboplatin (STELLAR 3)[24] or single-agent paclitaxel poliglumex versus either gemcitabine or vinorelbine (STELLAR 4).[25] In STELLAR 3, the median survival time and time to progression were 7.9 and 3.9 months, respectively, for paclitaxel poliglumex plus carboplatin and 8 and 4.6 months, respectively, for paclitaxel and carboplatin. In STELLAR 4, the median survival time and time to progression were 7.3 and 2.9 months, respectively, for paclitaxel poliglumex and 6.6 and 3.6 months, respectively for gemcitabine or vinorelbine. Although there was no difference in survival between the paclitaxel poliglumex-based regimens and the comparator regimens, these studies did show a better survival outcome in comparison with previous studies.

Mutations in the epidermal growth factor receptor (EGFR) are associated with a high response rate to EGFR tyrosine kinase inhibitors (TKIs) in patients with advanced NSCLC.[26,27] A phase II study in Japan evaluated first-line treatment with the EGFR-TKI gefitinib in patients with advanced NSCLC and a PS of 2 or higher who harbor EGFR mutations; it found a response rate of 66% and a median survival time of 17.8 months.[28] On the basis of these findings, treatment with EGFR-TKIs seems highly promising even in patients with a poor PS if they harbor EGFR mutations. However, most patients with advanced NSCLC, including those with a PS of 2, do not harbor such mutations. Cytotoxic chemotherapy, either single-agent or combination, thus remains the mainstay of treatment for this large subgroup of patients.

We found that doublet chemotherapy was associated with a substantial degree of toxicity in patients with advanced NSCLC and a PS of 2. Although nonplatinum-based doublet chemotherapy is thought to be less toxic than platinum-based doublet regimens and to be more favorable for the subgroup of patients for whom platinum-related toxicity is a concern,[29,30] the present study found that GV was not less toxic than CP in patients with a PS of 2. The frequency of anemia of grade 3 or 4 was higher in the GV arm than in the CP arm at a borderline level of significance (30.2% vs. 12.5%, P=0.05). There were also more treatment-related deaths in the GV arm than in the CP arm, suggesting that GV chemotherapy might not be feasible for this patient population. However, these findings must be interpreted with caution. The causes of death are often multifactorial in patients with advanced NSCLC, especially in those with a PS of 2, who are heterogeneous and whose poor PS is affected by tumor burden, comorbidity, or both. A limitation of the present study is that comorbidity was not assessed with a validated system such as the Charlson scale or the Cumulative Illness Rating Scale-Geriatric. A comprehensive assessment of comorbidity is thus warranted to evaluate its impact on treatment outcome and toxicity in patients with a PS of 2.

Neutropenia was the most prominent toxicity for both arms of the present study, with the prevalence of febrile neutropenia being similar in the 2 arms. Moreover, the frequencies of neutropenia and febrile neutropenia in the present study were similar to those in other studies of Japanese patients with a PS of 0 or 1.[8,30] Prophylactic use of granulocyte colony-stimulating factor was not permitted in the present study or in the previous studies. The frequencies of neutropenia and febrile neutropenia in the CP arm of the present study were higher than those observed in the ECOG 1599 study,[20] despite the fact that the doses of CP were identical in both trials. This apparent discrepancy may be attributable to ethnic differences including pharmacogenomic differences, which have been implicated in differences in toxicity of CP between patients with advanced NSCLC and a PS of 0 or 1 in Japan and those in the United States.[31]

Symptoms improved with treatment in both arms of the present study. Chemotherapy has previously been found to improve the quality of life in patients with advanced NSCLC and a PS of 2.[32] Given that the overall survival time for such patients is short, the aims of chemotherapy are to ameliorate symptoms and to improve the quality of life. Although symptom improvement alone does not represent an overall improvement in quality of life, our results suggest that doublet chemotherapy may be beneficial in patients with advanced NSCLC and a PS of 2 in terms of symptom improvement. However, evaluation of this benefit should take into account the substantial degree of toxicity.

In conclusion, the present study has shown that both platinum-based and nonplatinum-based doublet chemotherapeutic regimens are associated with a substantial level of toxicity as well as with a relatively short survival time, with a 1-year survival rate of <30%, in patients with advanced NSCLC and a PS of 2. On the basis of these findings, further evaluation of such doublet chemotherapy is not warranted in this patient population.

ACKNOWLEDGMENTS

The authors thank Yuki Inoue and Naomi Ohzumi for data management.

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Epidermal Growth Factor Receptor Mutation Status in Circulating Free DNA in Serum

From IPASS, a Phase III Study of Gefitinib or Carboplatin/Paclitaxel in Non-small Cell Lung Cancer

Koichi Goto, MD, PhD, Yukito Ichinose, MD,† Yuichiro Ohe, MD, PhD,‡ Nobuyuki Yamamoto, MD, PhD,§ Shunichi Negoro, MD,‖ Kazuto Nishio, MD, PhD,¶ Yohji Itoh, PhD,# Haiyi Jiang, MD,# Emma Duffield, MSc,** Rose McCormack, PhD,** Nagahiro Saijo, MD, PhD,¶ Tony Mok, MD,†† and Masahiro Fukuoka, MD, PhD¶*

Introduction: In IPASS (IRESSA Pan-Asia Study), clinically selected patients with pulmonary adenocarcinoma received first-line gefitinib or carboplatin/paclitaxel. This preplanned, exploratory analysis was conducted to increase understanding of the use of surrogate samples, such as serum, versus tumor biopsy samples for determining *EGFR* mutation status in the Japanese cohort ($n = 233$).

Methods: *EGFR* mutations were assessed using tumor tissue-derived DNA ($n = 91$) and circulating free (cf) DNA from pretreatment serum samples ($n = 194$).

Results: Fewer patients were *EGFR* mutation positive when assessed using pretreatment cfDNA (23.7%) versus tumor tissue-derived DNA (61.5%). cfDNA results identified no false positives but a high rate of false negatives (56.9%). There was a significant interaction between cfDNA *EGFR* mutation status and treatment for progression-free survival (PFS) ($p = 0.045$). PFS was significantly longer and objective response rate (ORR) higher with gefitinib than carboplatin/paclitaxel in the cfDNA *EGFR* mutation-positive subgroup (PFS: hazard ratio [HR], 0.29; 95% confidence interval [CI], 0.14–0.60; $p < 0.001$; ORR: odds ratio [OR], 1.71; 95% CI, 0.48–6.09; 75.0% versus 63.6%; $p = 0.40$). There was a slight numerical advantage in PFS and ORR for gefitinib over carboplatin/paclitaxel in the cfDNA *EGFR* mutation-negative subgroup, likely due to the high rate of false negatives within this subgroup.

Conclusions: These results merit further investigation to determine whether alternative sources of tumor DNA, such as cfDNA in serum, could be used for determining *EGFR* mutation status in future; currently, where a sample is available, analysis of tumor material is recommended.

Key Words: EGFR, Mutation, Gefitinib, NSCLC, Serum.

(*J Thorac Oncol.* 2012;7: 115–121)

*National Cancer Center Hospital East, Chiba; †National Kyushu Cancer Center, Fukuoka; ‡National Cancer Center Hospital, Tokyo; §Shizuoka Cancer Center, Shizuoka; ‖Hyogo Cancer Center, Hyogo; ¶Kinki University School of Medicine, Osaka; #AstraZeneca, Osaka, Japan; **AstraZeneca, Macclesfield, United Kingdom; and ††The Chinese University of Hong Kong, Shatin, Hong Kong.

Disclosure: K. Goto has received honoraria from AstraZeneca, Chugai Pharmaceutical Co., Ltd, and Ono Pharmaceutical Co., Ltd; S. Negoro and K. Nishio have received honoraria from AstraZeneca; Y. Itoh, H. Jiang, E. Duffield, and R. McCormack are employees of AstraZeneca and hold stock in the company; M. Fukuoka has received honoraria from AstraZeneca, Chugai Pharmaceutical Co., Ltd, Daiichi-Sankyo, and Ono Pharmaceutical Co., Ltd; T. Mok has acted as a consultant to AstraZeneca, Roche, Eli Lilly, Taiho Pharmaceutical Co., Ltd, Merck Serono, Boehringer Ingelheim, AVEO Pharmaceuticals Ltd, and Pfizer and has received honoraria from AstraZeneca, Roche, Eli Lilly, Boehringer Ingelheim, and Merck Serono and research funding from AstraZeneca.

Address for correspondence: Koichi Goto, Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwanoha, 6-5-1, Kashiwa, Chiba 277-8577, Japan. E-mail: kgoto@east.ncc.go.jp

Yuichiro Ohe is currently at National Cancer Center Hospital East, Chiba, Japan.

Presented in part at the 50th Annual Meeting of the Japan Lung Cancer Society, Tokyo, Japan, November 12–13, 2009; the European Organization for Research and Treatment of Cancer, the National Cancer Institute, and the American Society of Clinical Oncology (EORTC-NCI-ASCO) Annual Meeting, Brussels, Belgium, October 15–17, 2009; the 13th World Conference on Lung Cancer, July 31–August 4, 2009, San Francisco, CA, USA; the 49th Annual Meeting of the Japanese Respiratory Society, June 12–14, 2009; and the 45th Annual Meeting of the American Society of Clinical Oncology, May 29–June 2, 2009, Orlando, FL, USA.

ISSN: 1556-0864/12/0701-0115

The epidermal growth factor receptor (EGFR) superfamily has been implicated in the regulation of tumor cell biology and, as such, has emerged as a therapeutic target.[1] In 2004, mutations in the *EGFR* were reported to be associated with sensitivity to EGFR tyrosine kinase inhibitors (EGFR-TKIs).[2–4] The presence of such mutations in tumor tissue is associated with a number of clinical factors including Asian origin, female sex, adenocarcinoma histology, and a never-smoking history, and these factors have additionally been correlated with response to gefitinib (IRESSA, AstraZeneca, Macclesfield, UK), an EGFR-TKI.[5]

The IRESSA Pan-Asia Study (IPASS) compared gefitinib with carboplatin/paclitaxel as first-line treatment in 1217 never-smokers/light ex-smokers with advanced adenocarcinoma of the lung in East Asia.[6] Subgroup analysis of patients with *EGFR* mutations ($n = 261$) detected in DNA derived from tumor tissue samples demonstrated significantly longer progression-free survival (PFS) with gefitinib versus carboplatin/paclitaxel (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.36–0.64; $p < 0.001$).[6] In the *EGFR* mutation-negative (M−) subgroup ($n = 176$), PFS was significantly longer with carboplatin/paclitaxel versus gefitinib (HR, 2.85; 95% CI, 2.05–3.98; $p < 0.001$). Objective response rates (ORR) were 71.2% versus 47.3% ($p < 0.001$) and 1.1% versus 23.5% ($p = 0.001$) with gefitinib versus carboplatin/paclitaxel in *EGFR* M+ and M− patients, respectively.

The difficulties of collecting sufficient tumor tissue for biomarker analyses have stimulated interest in analyses using surrogate samples, such as serum and plasma samples, which frequently contain circulating free (cf) DNA derived from tumor tissues. Previous studies in relatively few patients had detected *EGFR* mutations in cfDNA in serum or plasma samples and suggested that using such methodology to predict response to gefitinib was worthy of further evaluation.[7–12] However, most of these studies were retrospective.

Herein, we report the evaluation of *EGFR* mutations in cfDNA from serum samples of patients in the IPASS study recruited in Japan. This preplanned, exploratory analysis was conducted to increase the understanding of the use of surrogate samples, such as serum, versus tumor biopsy samples for determining *EGFR* mutation status.

MATERIALS AND METHODS

Study Design and Patients

Full details of the IPASS study design (ClinicalTrials.gov identifier NCT00322452) have been published previously.[6] Planned objectives of this substudy of IPASS were evaluations of efficacy between the gefitinib and carboplatin/paclitaxel treatment groups by cfDNA *EGFR* mutation status from pretreatment serum samples and evaluation of the concordance between *EGFR* mutation status in pretreatment cfDNA versus tumor. Comparison of *EGFR* mutation status in pretreatment versus postprogression serum samples was also performed; however, not all patients with a pretreatment sample had a postprogression sample, which limited the comparison. In addition, comparisons with postprogression serum and pretreatment pleural effusion samples are reported in Supplemental Digital Content 1 (Methods http://links.lww.com/JTO/A152). Preplanned analysis of the Japanese subset of the IPASS population was performed to meet Japanese regulatory requirements.

All patients provided written informed consent. Provision of samples for biomarker research was optional and involved separate consent procedures for tumor and serum sampling. An independent ethics committee at each participating institution approved the study protocol. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, applicable regulatory requirements, and AstraZeneca's policy on bioethics.

Biomarker Analyses

Sample collection and DNA extraction are described in Supplemental Digital Content 1 (Methods http://links.lww.com/JTO/A152). *EGFR* mutations were detected using the DxS *EGFR* Mutation Test Kit for Research Use Only (DxS, Manchester, UK), which combines Amplification Refractory Mutation System (ARMS) (allele-specific polymerase chain reaction [PCR]) with the Scorpions real-time PCR technology.[13,14] Modified run conditions and cutoffs (delta Ct values [dCt]) used to define M+ samples for cfDNA derived from serum and pleural effusion samples were as follows: 50 cycles of PCR were carried out and the dCt for exon 19 deletions was 12, L858R was 14, and T790M was 8 (for tumor DNA, 40 cycles of PCR were carried out and the dCt cutoffs were 9, 11, and 8, respectively). In analyses of tumor DNA, all 29 mutations detected by the kit were assayed (19 deletions in exon 19, L858R, T790M, L861Q, G719X [S, A, or C], S768I, and 3 insertions in exon 20); whereas for serum and pleural effusion samples, the 21 most common mutations (19 deletions in exon 19, L858R, and T790M) were assayed (to make the best use of limited cfDNA yield). Samples were tested in duplicate, and only if both replicates were positive for at least one of the mutations was the sample defined as M+. Patients without a tumor sample evaluable for mutation analysis and samples which were not successfully analyzed were classified as *EGFR* mutation unknown. Biomarker samples were assayed blinded to clinical outcome and randomized treatment.

Statistical Analyses

Serum samples were collected for patients recruited in Japan and who consented to this optional analysis. Analyses of efficacy end points comparing treatment groups in the Japanese subset (intent-to-treat [ITT] population) were assessed as described previously for the overall IPASS population.[6] However, for the analyses in the cfDNA M+ and M− subgroups, the prespecified covariates of World Health Organization (WHO) performance status (PS), smoking history, and sex could not be included as covariates because of the small number of patients who had a WHO PS 2, were ex-smokers, or were males; therefore, models without covariates were used. Because of the lack of power to detect treatment differences, the result of the Japanese subset should be interpreted with caution, taking into account the associated variability and overlap in plausible range of effects (CIs). Analyses comparing treatment groups were performed for PFS (by Cox proportional hazards model) and ORR (by logistic regression model) in subgroups defined by cfDNA *EGFR* mutation status. A test for interaction between cfDNA *EGFR* mutation status (M+ or M−) and treatment was used to assess whether the PFS treatment effect was statistically different between subgroups.

Comparison of pretreatment cfDNA versus tumor *EGFR* mutations was based on the 21 mutations analyzed for cfDNA using patients with known mutation status (M+ or M−) in both samples. The sensitivity, specificity, positive

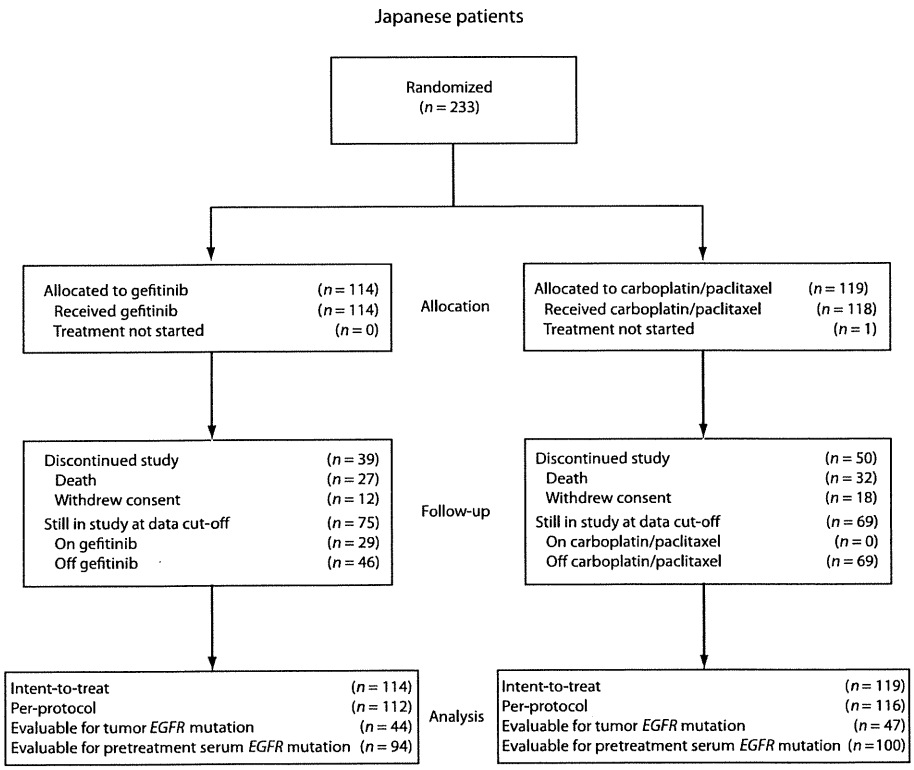

FIGURE 1. CONSORT diagram representing patient disposition (including number of patients with tumor tissue or serum evaluable for *EGFR* mutation status). *EGFR*, epidermal growth factor receptor.

and negative predictive values and their exact 95% CIs, and the kappa coefficient and 95% CI, for *EGFR* mutation status in serum samples, were evaluated assuming that the *EGFR* mutation status in tumor tissue was a true reflection of tumor biology. The proportion of concordance between cfDNA and tumor was calculated on a similar basis by excluding patients judged as unknown using either cfDNA or tumor samples.

RESULTS

Patients

In total, 233 patients from Japan were randomized to study treatment (19.1% of the overall IPASS population). Preplanned evaluations of efficacy, quality of life, and safety for the overall Japanese study population have been previously presented[15,16] and are summarized in Supplemental Digital Content 2 (Results http://links.lww.com/JTO/A153) and 3 (Figure http://links.lww.com/JTO/A154). The patient disposition for the Japanese subset of IPASS is shown in Figure 1.

EGFR Mutation Status

An evaluable DNA sample for *EGFR* mutation status derived from tumor tissue was available for 91 patients; of these, 56 (61.5%) patients were *EGFR* M+, with a lower proportion of *EGFR* M+ patients in the gefitinib group compared with the carboplatin/paclitaxel group (52.3% [23/44] versus 70.2% [33/47]) (Figure 2). A total of 194 patients provided a pretreatment serum sample for mutation analysis; all were evaluable. Of these, 46 (23.7%) patients were cfDNA *EGFR* M+ (25.5% [24/94] and 22.0% [22/100] in the gefitinib and carboplatin/paclitaxel groups, respectively) (Figure 2). Data from pretreatment pleural effusion (9 patients) and postprogression serum analyses (144 patients) are presented in Supplemental Digital Content 2 (Results http://links.lww.com/JTO/A153) and 4 (Table http://links.lww.com/JTO/A155).

Demographic and Baseline Characteristics of Patients with Known *EGFR* Mutation Status

Key demographic and baseline characteristics for patients with known (i.e., evaluable) cfDNA or tumor *EGFR* mutation status were generally consistent with the overall Japanese study population (Table 1).

Pretreatment cfDNA *EGFR* Mutation Status and Clinical Outcomes

The subset of patients with known cfDNA *EGFR* mutation status could be assumed to be representative of the overall Japanese study population (and therefore the overall study population) as shown by similar PFS and ORR results (Table 1).

A significant interaction between cfDNA *EGFR* mutation status and treatment was evident for PFS (interaction test $p = 0.045$). PFS was significantly longer with gefitinib than carboplatin/paclitaxel in the cfDNA *EGFR* M+ subgroup (HR, 0.29; 95% CI, 0.14–0.60; $p < 0.001$) (Figure 3*A*). In the cfDNA *EGFR* M− subgroup, there were no significant differences for PFS with gefitinib compared with carboplatin/paclitaxel (HR, 0.88; 95% CI, 0.61–1.28; $p = 0.50$) (Figure 3*B*). However, the HR was not constant over time. We