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ORIGINAL ARTICLE

A dose-finding and pharmacokinetic study of nedaplatin in elderly patients with advanced non-small cell lung cancer

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Abstract
Purpose Nedaplatin is a second-generation platinum showing favorable activity against non-small cell lung cancer (NSCLC). Dose-limiting toxicity (DLT) is thrombocytopenia, predicted by creatinine clearance (Ccr). This study was conducted to determine the recommended dose, and evaluate the toxicities, pharmacokinetics and efficacy for elderly NSCLC patients.
Methods Patients ≥70 years were stratified into two groups based on renal functions: Group A, Ccr ≥ 60 and Group B, 40 ≤ Ccr < 60. The initial doses were 80 and 60 mg/m^2 in Groups A and B, respectively. The doses were escalated in 20-mg/m^2 increments to 100 mg/m^2 until DLT.
Results Chemotherapy-naïve 39 elderly patients (Group A/Group B: 22/17) received a total of 83 cycles. Major toxicities were hematological. In Group A, one of the 15 patients at 100 mg/m^2 experienced DLT (neutropenia) and the recommended dose was determined at 100 mg/m^2. In Group B, three of the five patients had DLTs (leukopenia, neutropenia, thrombocytopenia and febrile neutropenia) at 100 mg/m^2, and the recommended dose was determined at 80 mg/m^2. The percentage decreases of neutrophil were well correlated with total and free-Pt AUCs. Partial responses were observed in 13 (33%) of the 39 patients, and 12 of the 13 patients who responded had a squamous cell carcinoma.
Conclusions Nedaplatin was administered simply and feasibly by stratifying renal function and exerted favorable antitumor activity for elderly patients with NSCLC, especially on squamous cell carcinoma.

Keywords Nedaplatin · Dose-finding study · Pharmacokinetics · NSCLC · Elderly patient

Introduction

The proportion of elderly patients with non-small cell lung cancer (NSCLC) is increasing [1]. At present, the first-line standard chemotherapy for non-elderly patients with advanced NSCLC is a platinum-based doublet regimen. The efficacy and feasibility of this strategy have been demonstrated in several randomized trials in patients with a good performance status and aged ≤70 years [2–4]. However, platinum-based doublet regimens are not always feasible for elderly patients. Age-related comorbidity and physiologic changes increase inter-individual pharmacokinetic variability, possibly leading to unacceptable severe toxicities. In particular, application of a cisplatin-based regimen to elderly patients is substantially restricted because of the risk of emesis, neurotoxicity and nephrotoxicity.

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Oshita et al. [5] prospectively evaluated the feasibility of cisplatin-based chemotherapy in patients aged 75 years or older. Only 10 (29%) out of the 34 patients fulfilled the eligibility criteria for the cisplatin-based regimen. Furthermore, the majority of these eligible patients had grade 4 neutropenia and infectious episodes requiring antibiotics. In another analysis of cisplatin pharmacokinetics, the area under the plasma concentration versus time curve (AUC) of the ultrafilterable and total plasma platinum increased with age, and this was an independent predictor of cisplatin pharmacokinetics [6]. Therefore, the administration of cisplatin is restricted to highly select elderly patients.

(Glycolate-*O,O'*)-diammine platinum (II) (nedaplatin) is a second-generation platinum analog synthesized by Shionogi & Co., Ltd. (Osaka, Japan). In the preclinical studies, nedaplatin is highly active against solid tumors and has higher aqueous solubility than cisplatin [7–9]. The emesis and nephrotoxicity of nedaplatin are substantially reduced, compared with those of cisplatin, and multiple days of hydration for renal protection are not required [10]. Dose-limiting toxicity (DLT) is thrombocytopenia, and recommended dose in Japanese patient ≤70 years is 100 mg/m^2 every 4 weeks. This agent is active against NSCLC, with a response rate of 20.5% for previously untreated patients [10]. In a pharmacokinetic analysis, thrombocytopenia was significantly correlated with renal function (i.e., creatinine clearance [Ccr]), and nadir platelet count could be predicted from the following formula [11]:

$$[\text{Nadir platelet count}]\left(/\text{mm}^3\right) = -64,264.7 + 2,783.4 \times [\text{Ccr}](\text{mL/min})$$

We conducted a dose-finding and pharmacokinetic study of nedaplatin in elderly patients with NSCLC, stratified into two groups based on renal function. This study was conducted to determine the recommended dose, and evaluate the toxicity profiles, pharmacokinetics and antitumor activity.

Patients and methods

Eligibility

Patients with histologically and cytologically confirmed chemotherapy-naïve advanced or metastatic non-small cell lung cancer were eligible for this study. Other eligibility criteria included the following: (1) age ≥70 years; (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (3) adequate bone marrow (white blood cell [WBC] count ≥4,000/mm^3, absolute neutrophil count [ANC] ≥2,000/mm^3, hemoglobin level ≥9.0 g/dL and platelet [PLT] count ≥100,000/mm^3), hepatic (serum total bilirubin level ≤1.5 mg/dL, serum asparatate aminotransferase [AST] level ≤100 IU/L and serum alanine aminotransferase [ALT] level ≤100 IU/L), renal (serum creatinine [Cr] level ≤1.5 mg/dL, creatinine clearance [Ccr] ≥40 mL/min) and pulmonary (PaO_2 ≥60 torr) functions.

The exclusion criteria were as follows: (1) symptomatic brain metastasis; (2) pleural or pericardial effusions and ascites requiring drainage; (3) serious pre-existing medical conditions such as uncontrolled infections, severe heart disease, uncontrolled diabetes and psychogenic disorders; and (4) hepatic B or C virus or human immunodeficiency virus infection.

Written informed consent was obtained from all the patients. This study was approved by the Institutional Review Board of the National Cancer Center.

Study design, dosage and dose escalation

This study was designed to determine the recommended dose of nedaplatin for elderly patients with advanced NSCLC, stratified into two groups based on renal function. The primary objective was to determine the recommended dose, and the secondary objectives were to evaluate toxicity profiles, pharmacokinetics and antitumor activity.

Patients were stratified into two groups based on their renal function at the time of study entry: Group A, Ccr ≥60 mL/min; and Group B, 40 ≤ Ccr < 60 mL/min. Ccr was measured on three consecutive days, and the mean value was used for stratification. Each Ccr was calculated using the following formula:

$$\text{Ccr}\,(\text{mL/min}) = [\text{urine volume}\,(\text{mL/min}) \times \text{urine creatinine}\,(\text{mg/dL})]/\text{serum creatinine}\,(\text{mg/dL})$$

In Group A, the initial dose of nedaplatin was 80 mg/m^2, and this was escalated to 100 mg/m^2. In Group B, the initial dose was 60 mg/m^2, and this was escalated to 80 and 100 mg/m^2. At least three to six patients were enrolled at each dose level, and the unacceptable dose was defined as the dose level at which >50% of the patients experienced DLT. The definition of DLT was as follows: (1) ≥grade 3 leukopenia, neutropenia or thrombocytopenia; (2) ≥grade 3 non-hematological toxicities except for alopecia, nausea and vomiting; (3) ≥grade 3 nausea and vomiting for ≥5 days. The recommended dose was defined as one dose level below the unacceptable dose level in each treatment arm.

Nedaplatin administration

Nedaplatin (Aqupla, (glycolate-*O,O'*)-diammine platinum (II); Shionogi Pharmaceutical Company, Osaka, Japan) was obtained commercially. Premedication, consisting of

3 mg of granisetron and 16 mg of dexamethasone diluted in 100 mL of 0.9% saline, was administered via a 30-minute intravenous (IV) infusion. The calculated doses of nedaplatin in both treatment groups were diluted in 300 mL of 0.9% saline and were administered using a 1-h IV infusion every 4 weeks. Following the nedaplatin administration, 500 mL of 0.9% saline was administered intravenously to provide minimal hydration.

Pretreatment and follow-up evaluation

On enrollment into the study, history and physical examination was performed. Complete differential blood cell count (including WBC count, ANC, hemoglobin and PLT), and clinical chemistry analysis (including serum total protein, albumin, bilirubin, Cr, AST, ALT, gamma-glutamyltransferase, and alkaline phosphatase) were performed. These above were performed at least twice a week throughout the study. Tumor measurement was planned every cycle, and antitumor response was assessed using the WHO standard response criteria. Toxicity was evaluated according to the National Cancer Institute common toxicity criteria (version 2.0).

PK study

Pharmacokinetic (PK) evaluations were performed in all patients during the initial cycle of treatment. Heparinized venous blood samples (7 mL) were taken before infusion, at 30 min and just before the end of infusion, as well as at 15 and 30 min and 1, 2, 3, 5, 7, 11, 23 and 47 h after the end of infusion.

Blood samples were centrifuged immediately at 4,000 rpm for 10 min. One milliliter of plasma was stored at −20°C or below in a polyethylene tube until the measurement of total plasma platinum (total-Pt) concentration. Residual plasma was transferred to an Amicon Centrifree tube (Amicon, Inc., Beverly, MA, USA) and centrifuged at 4,000 rpm for 20 min. Ultrafiltrate of the plasma was taken and stored at −20°C or below in a polyethylene tube until the measurement of the plasma-free platinum (free-Pt) concentration. The total-Pt and free-Pt concentrations were measured using flameless atomic absorption spectrometry, as previously reported [12].

The PK parameters were estimated using a nonlinear least-squares regression analysis (WinNonlin, Version 5.2; Bellkey Science, Inc., Chiba, Japan) with a weighting factor of $1/\text{year}^2$. The individual plasma concentration–time data were fitted to one-, two- and three-exponential equations using a zero-order infusion input and first-order elimination (corresponding to a one-, two- and three-compartment PK model). The model was chosen on the basis of Akaike's information criteria [13]. Fitted parameters (coefficients and exponent of exponential equations) were permitted in the computation of the following PK parameters: half life ($t_{1/2}$), area under the plasma concentration versus time curve (AUC), systemic clearance (CL), and volume of distribution at steady state (V_{dss}).

To assess the pharmacodynamic effect, percentage decrease was calculated in WBC, ANC or PLT according to the following formula:

$$\text{Percentage decrease} = [(\text{pretreatment count} - \text{nadir count})/(\text{pretreatment count})] \times 100.$$

These percentages were related to the AUC according to the sigmoid E_{max} model, as follows:

$$\text{Effect}(\%) = [E_{max}(\text{AUC})^k]/[\text{AUC}_{50}^k + \text{AUC}^k] \times 100.$$

A nonlinear least-squares regression using WinNonlin was used to estimate the AUC that produces 50% of the maximum effect (AUC_{50}) and the sigmoidicity coefficient (k).

Results

Patient characteristics

Between June 1996 and July 2001, 39 patients were stratified into two groups (22 in Group A and 17 in Group B) based on their renal functions at entry into the study (Table 1). They received a total of 83 cycles of therapy. The patients comprised 35 males and 4 females with good performance status, and the median age was 76 years in both treatment groups. All the patients were included in the toxicity evaluation. A total of 28 (72%) patients were included in the PK analysis and the remaining 11 (28%) were excluded because of insufficient PK samplings. Eight patients (two from Group A and six from Group B) had stage IIIA disease, but were not candidates for thoracic radiotherapy because of their poor pulmonary function. Six patients (five from Group A and one from Group B) received surgical resections for primary tumors. As much as 21 patients (54%, 12 from Group A and 9 from Group B) had squamous cell carcinoma. Nine patients (4 from Group A and 5 from Group B) received only one cycle of therapy because of progressive disease (PD) and 22 patients (12 from Group A and 10 from Group B) received two cycles of treatment. Among these 22 patients, partial response (PR), stable disease (SD) and PD were observed in 8, 10 and 4 patients, respectively. Five of eight patients with PR, two of ten with SD and one of four with PD received sequential thoracic radiotherapy for primary lesion following two cycles of treatment. Two of ten patients with SD and one of four with PD received palliative

radiotherapy for metastatic lesion. Two of four patients with PD received second-line chemotherapy. The remaining nine patients received supportive care according to the patients' request.

Toxicity

All the 39 patients were included in the toxicity evaluation. Major toxicities were hematological, such as leukopenia, neutropenia and thrombocytopenia, in both groups, and these hematological toxicities increased in severity with increased dose level of nedaplatin. In Group A, 1 (6.7%) out of the 15 patients treated at a dose level of 100 mg/m^2 had grade 3 neutropenia; this dose level was considered to be acceptable (Table 2). In Group B, three (50%) out of six patients treated at a dose level of 80 mg/m^2 had ≥grade 3 hematological toxicities (one with grade 3 neutropenia, another with grade 4 neutropenia and febrile neutropenia, and the other with grade 3 leukopenia, anemia and grade 4 thrombocytopenia). The patient with grade 4 thrombocytopenia required a platelet transfusion. At a dose level of 100 mg/m^2, three (60%) out of five patients had ≥grade 3 hematological toxicities (one with grade 3 leukopenia and neutropenia, another with grade 3 thrombocytopenia and grade 4 neutropenia, and the other with grade 3 leukopenia, thrombocytopenia and grade 4 neutropenia). These three patients had also febrile neutropenia. In Group B, a dose level of 100 mg/m^2 was considered to be unacceptable (Table 2).

Non-hematological toxicities, mainly nausea and anorexia, were generally mild in severity and were not dose limiting in either group (Table 3). Renal toxicity,

Table 1 Patient characteristics

	Group A (Ccr ≥60 mL/min)		Group B (40 ≤ Ccr < 60 mL/min)	
	No. of patients	Percentage	No. of patients	Percentage
Total patients enrolled	22	100	17	100
Assessable for toxicity	22	100	17	100
Assessable for PK analysis	15	68	13	76
Age, median (range), years	76 (70–82)		76 (70–78)	
Sex				
Male	19	86	16	94
Female	3	14	1	6
ECOG PS				
0	6	27	1	6
1	16	73	15	88
2	0	0	1	6
Stage				
IIIA	2	9	6	35
IIIB	4	18	6	35
IV	11	50	4	24
Postoperative recurrence	5	23	1	6
Pathological subtype				
Squamous cell carcinoma	12	54	9	53
Adenocarcinoma	9	41	8	47
P/D carcinoma	1	5	0	0
Dose of nedaplatin (mg/m^2)				
60	–	–	6	35
80	7	32	6	35
100	15	68	5	30
Treatment cycle				
Median (range)	2 (1–5)		2 (1–4)	
1 cycle	4	18	5	29
2 cycles	12	55	10	59
≥3 cycles	6	27	2	12

PK pharmacokinetics, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *P/D carcinoma* poorly differentiated carcinoma

Table 2 Hematological toxicity

Group A (Ccr ≥60 mL/min)	Dose level (mg/m^2), (number of patients)									
	80 (n = 7) Grade					100 (n = 15) Grade				
Event	0	1	2	3	4	0	1	2	3	4
Leukopenia	6	1	0	0	0	12	1	2	0	0
Neutropenia	6	1	0	0	0	8	4	2	1[a]	0
Anemia	4	2	1	0	0	5	7	3	0	0
Thrombocytopenia	7	0	0	0	0	12	2	1	0	0
No. of patients with febrile neutropenia	0					0				
No. of patients with DLT	0					1				

Group B (40 ≤ Ccr < 60 mL/min)	Dose level (mg/m^2), (number of patients)														
	60 (n = 6) Grade					80 (n = 6) Grade					100 (n = 5) Grade				
Event	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Leukopenia	5	1	0	0	0	2	1	2	1[a]	0	2	0	1	2[a]	0
Neutropenia	5	1	0	0	0	2	2	0	1[a]	1[a]	1	1	0	1[a]	2[a]
Anemia	4	1	1	0	0	3	1	1	1[a]	0	1	2	2	0	0
Thrombocytopenia	6	0	0	0	0	3	1	1	0	1[a]	2	1	0	2[a]	0
No. of patients with febrile neutropenia	0					1					3				
No. of patients with DLT	0					3					3				

[a] DLT

characterized as an increase in Cr, was also mild, and only one out of five patients treated at a dose level of 100 mg/m^2 in Group B had a grade 2 Cr increase. Considering the toxicity profiles, the recommended doses in Groups A and B were determined to be 100 and 80 mg/m^2, respectively.

Response and survival

The antitumor response was assessed in all the 39 patients (Table 4). Of the 39 patients who achieved PR, 13 had an overall response rate of 33%. Similar antitumor responses were observed in both treatment groups; that is, 6 (27%) of 22 and 7 (41%) of 17 patients had PRs in Groups A and B, respectively. Furthermore, 12 of the 13 patients with PRs in both groups had squamous cell carcinoma, and the response rate among patients with squamous cell carcinoma was 57%. Survival follow-up was completed in all the enrolled patients. The median survival time was 11.2 months (95% confidence interval: 7.7–14.6 months), and the 1-, 2- and 5-year survival rates were 46, 23 and 5%, respectively.

Pharmacokinetics

Pharmacokinetic analysis was performed using data from 28 (72%) of the 39 patients. The first patient enrollment in both treatment groups was started in 1996, and techniques of the sample centrifuging and measurement were not fully developed at the beginning of this pharmacokinetic study. Therefore, the remaining 11 patients (28%) were excluded for pharmacokinetic analysis. The mean plasma concentration–time profiles of total-Pt and free-Pt of nedaplatin are illustrated in Fig. 1. The plasma disappearances of total-Pt and free-Pt were biphasic, and the mean terminal half lives in all the assessable patients averaged 6.28 and 3.57 h, respectively. The C_{max} and AUC of the total-Pt and free-Pt tended to increase with the dose of nedaplatin. The AUCs of the total- and free-Pt at a dose of 100 mg/m^2 in Group A seemed similar to those at a dose of 80 mg/m^2 in Group B (Table 5), and there were no significant differences between these two treatment subgroups (P = 0.293 for total-Pt AUC and P = 0.336 for free-Pt AUC). Furthermore, the AUCs of free-Pt at the recommended doses in both groups (i.e., 100 mg/m^2 in Group A and 80 mg/m^2 in Group B) seemed also similar to that in patients aged 70 years or under who had been treated with 100 mg/m^2 of nedaplatin [14]. In the sigmoid Emax model assessing the pharmacodynamic effect of nedaplatin, the percentage decrease in the neutrophil counts were well correlated with the total-Pt (r = 0.652) and free-Pt (r = 0.723; Fig. 2).

Table 3 Non-hematological toxicity

Group A (Ccr ≥60 mL/min)	Dose level (mg/m^2), (number of patients)									
	80 (n = 7) Grade					100 (n = 15) Grade				
Event	0	1	2	3	4	0	1	2	3	4
Nausea	5	1	1	0	0	3	9	3	0	0
Vomiting	6	1	0	0	0	15	0	0	0	0
Anorexia	5	1	1	0	0	7	4	4	0	0
Diarrhea	6	1	0	0	0	14	1	0	0	0
Stomatitis	7	0	0	0	0	15	0	0	0	0
Hyperbilirubinemia	6	0	1	0	0	15	0	0	0	0
AST increase	6	1	0	0	0	13	2	0	0	0
ALT increase	6	1	0	0	0	13	2	0	0	0
ALP increase	7	0	0	0	0	15	0	0	0	0
Cr increase	7	0	0	0	0	15	0	0	0	0

Group B (40 ≤ Ccr < 60 mL/min)	Dose level (mg/m^2), (number of patients)														
	60 (n = 6) Grade					80 (n = 6) Grade					100 (n = 5) Grade				
Event	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Nausea	1	4	1	0	0	1	3	2	0	0	1	1	3	0	0
Vomiting	6	0	0	0	0	5	1	0	0	0	5	0	0	0	0
Anorexia	4	2	0	0	0	1	3	2	0	0	1	1	3	0	0
Diarrhea	6	0	0	0	0	5	1	0	0	0	5	0	0	0	0
Stomatitis	6	0	0	0	0	6	0	0	0	0	5	0	0	0	0
Hyperbilirubinemia	6	0	0	0	0	6	0	0	0	0	4	0	1	0	0
AST increase	4	2	0	0	0	5	0	1	0	0	4	0	1	0	0
ALT increase	5	1	0	0	0	5	0	1	0	0	4	0	1	0	0
ALP increase	6	0	0	0	0	5	1	0	0	0	5	0	0	0	0
Cr increase	6	0	0	0	0	4	2	0	0	0	4	0	1	0	0

AST asparatate aminotransferase, *ALT* serum alanine aminotransferase, *ALP* alkaline phosphatase, *Cr* creatinine

Discussion

In this dose-finding study, we evaluated the toxicities, pharmacokinetics as well as antitumor activity, and determined the recommended doses of nedaplatin for elderly patients with advanced NSCLC based on renal function. The predominant toxicities were hematological, such as leukopenia, neutropenia and thrombocytopenia, in both groups. These hematological toxicities tended to increase in severity with the increased dose level of nedaplatin. Non-hematological toxicities were acceptable and those were not dose limiting in either group. The recommended dose was determined as 100 mg/m^2 every 4 weeks in elderly patients with a renal function of Ccr ≥ 60 mL/min, which is the same dose recommended for patients aged ≤70 years. On the other hand, for elderly patients with a renal function of 40 ≤ Ccr < 60 mL/min, the recommended dose was 80 mg/m^2 every 4 weeks. In this study,

Table 4 Response

Group	Dose level (mg/m^2)	No. of patients	Response				PR	
			CR	PR	SD	PD	Sq.	Non–sq.
Group A (Ccr ≥60 mL/min)	80	7	0	2	3	2	2	0
	100	15	0	4	6	5	4	0
Group B (40 ≤ Ccr < 60 mL/min)	60	6	0	3	2	1	2	1
	80	6	0	3	1	2	3	0
	100	5	0	1	1	3	1	0
Total		39	0	13	13	13	12	1

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *Sq.* squamous cell carcinoma, *Non-sq.* non-squamous cell carcinoma

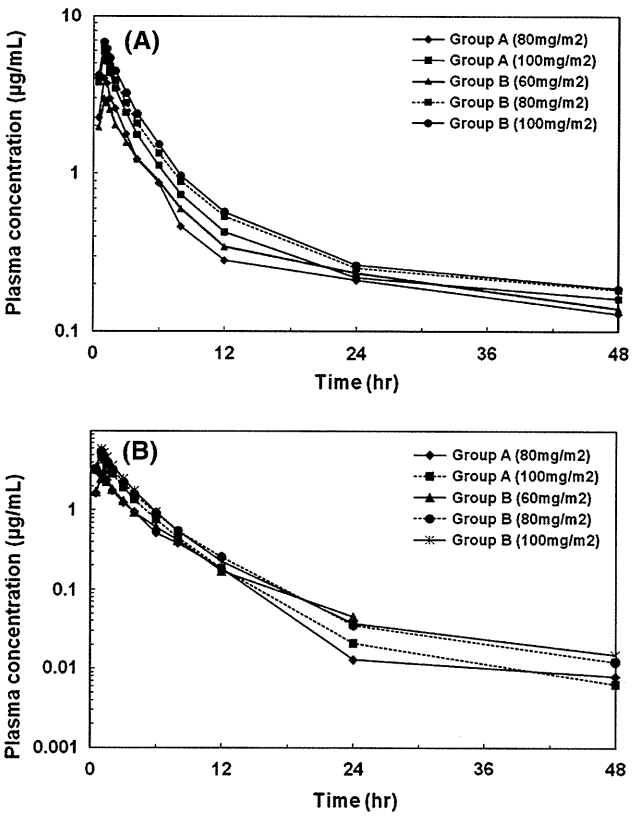

Fig. 1 Mean plasma concentration–time profiles for: **a** total-Pt and **b** free-Pt of nedaplatin

an additional nine patients were enrolled at the dose level of 100 mg/m^2 in Group A. First, the favorable antitumor response was observed in squamous cell carcinoma and we intended to evaluate the antitumor response mainly for squamous cell carcinoma. Then, five of nine additional patients enrolled had squamous cell carcinoma. Second, the recommended dose was determined as 100 mg/m^2 in Group A, which was the same dose in younger patients. We intended to confirm the toxicity and pharmacokinetic profiles in this elderly subgroup.

In the development of chemotherapy for elderly patients, the selection of appropriate agents is extremely important. Candidate agents must have confirmed antitumor activities and acceptable toxicity profiles in younger patients (e.g., aged ≤70 years). In this study, we investigated nedaplatin as it had a lower incidence of associated emesis and nephrotoxicity, compared with cisplatin, and favorable antitumor activity in NSCLC patients aged ≤70 years. Furthermore, the current standard treatment for elderly patients with advanced NSCLC, that is, third-generation single-agent chemotherapy such as vinorelbine, gemcitabine or docetaxel, had not been established at the time of planning of the study [15–17]. The DLT of nedaplatin in patients aged ≤70 years was reported to be thrombocytopenia, which is correlated with renal function; therefore, we expected that nedaplatin could be safely administered to elderly patients by stratifying the patients according to renal function. Patients with a Ccr ≥40 mL/min were eligible for inclusion in this study based on the results of a previous PK analysis examining the correlation between the nadir platelet count and renal function (described in "Introduction") [11]. When younger patients with a Ccr ≥40 mL/min were treated with 100 mg/m^2 of nedaplatin, the predicted nadir platelet count was ≥50,000/mm^3. Therefore, the initial doses of nedaplatin in Group A (Ccr ≥60 mL/min) and Group B (40 ≤ Ccr < 60 mL/min) were determined to be 80 and 60 mg/m^2, respectively. The dose escalation over 100 mg/m^2 was not planned, because the recommended dose in younger patients (aged ≤70 years) had already been determined at 100 mg/m^2.

In this study, milder criteria of DLT was applied, compared with that used in conventional phase I studies. In this developmental strategy, we pursued "the recommended dose with moderate and acceptable toxicities for the majority of elderly patients", instead of "the recommended dose with the severe toxicities in a small and limited number of patients, as per most conventional phase I studies", because the physiological and pharmacological function of elderly patients is highly variable.

Table 5 Pharmacokinetic parameters of total-Pt and free-Pt

Group	Dose level (mg/m^2)	No. of patients	No. of assessables for PK analysis	C_{max} (μg/mL)	AUC (μg/mL h)	V_{dss} (L)	$T_{1/2}$ (h)	CL (L/h)
PK parameters of total-Pt								
Group A (Ccr ≥60 mL/min)	80	7	2[a]	4.02 (3.49, 4.57)	22.58 (13.46, 31.69)	64.24 (35.27, 93.21)	14.15 (3.25, 25.04)	6.00 (3.60, 8.40)
	100	15	13	5.94 ± 1.38	21.65 ± 4.54	31.50 ± 13.40	3.28 ± 1.35	7.63 ± 1.74
Group B (40 ≤ Ccr < 60 mL/min)	60	6	2[a]	3.02 (2.91, 3.12)	19.78 (14.87, 24.68)	57.05 (33.21, 80.89)	10.77 (4.08, 17.46)	5.21 (4.16, 6.25)
	80	6	6	6.35 ± 1.11	25.99 ± 9.68	29.29 ± 13.18	7.88 ± 8.97	6.10 ± 1.13
	100	5	5	6.83 ± 1.20	32.11 ± 7.86	32.84 ± 22.00	6.62 ± 4.55	5.01 ± 1.57
PK parameters of free-Pt								
Group A (Ccr ≥60 mL/min)	80	7	2[a]	2.72 (2.13, 3.31)	10.56 (7.05, 14.06)	42.30 (37.98, 46.62)	3.49 (2.70, 4.28)	12.08 (8.11, 16.04)
	100	15	13	5.11 ± 1.51	16.20 ± 3.34	32.26 ± 11.17	3.51 ± 4.02	10.26 ± 2.46
Group B (40 ≤ Ccr < 60 mL/min)	60	6	2[a]	2.55 (2.46, 2.64)	11.59 (11.38, 11.79)	49.33 (33.22, 65.43)	6.16 (2.98, 9.34)	8.45 (7.89, 9.01)
	80	6	6	5.52 ± 1.25	18.53 ± 7.12	29.51 ± 9.11	3.40 ± 0.65	7.25 ± 2.21
	100	5	5	5.91 ± 1.21	20.69 ± 5.52	29.63 ± 12.32	2.92 ± 0.66	7.87 ± 2.71
Patients ≤70 years [14]	100	5	5		15.9			

Data are shown as mean ± SD excepting the dose level of 80 mg/m^2 in Group A and 60 mg/m^2 in Group B

PK pharmacokinetics, *total-Pt* total platinum, *free-Pt*, free platinum, C_{max} maximum plasma concentration, *AUC* area under the plasma concentration versus time curve, V_{dss} volume of distribution at steady-state, $T_{1/2}$ terminal half life, *CL* systemic clearance

[a] Data are shown as mean (actual data)

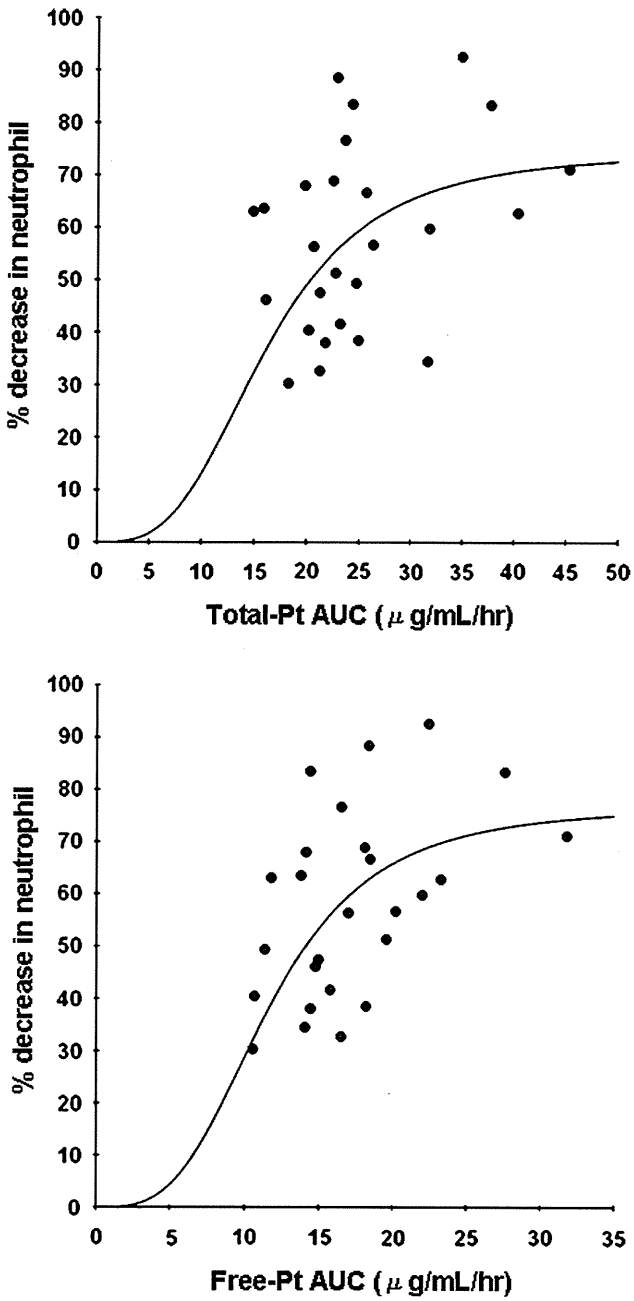

Fig. 2 Relationship between AUCs of total/free-Pt and the percentage decrease in the neutrophil count

In the pharmacokinetic analysis, the free-Pt AUC at a dose of 100 mg/m^2 in Group A seemed similar to that of 80 mg/m^2 in Group B, and there was no significant difference between these two treatment subgroups ($P = 0.336$). These results endorsed an almost equivalent drug exposure in both patient groups, stratified according to renal function. Furthermore, the AUC values in both groups seemed similar to historical data (obtained in a study with a small sample size) for patients aged ≤70 years [14]. However, a significant correlation was not observed between the renal function (i.e., the Ccr value) and the nadir platelet count, as in a previous report examining younger patients. These were possibly attributed to the wide inter-patient physiological and pharmacological variability among elderly patients or just the consequence of the adaptation of dose [11]. For elderly patients, a strict dose calculation of nedaplatin based on renal function, such as the dose calculation for carboplatin using the Calvert formula [18], is not required, and a simple dose selection of nedaplatin stratified according to renal function is considered to be reasonable.

A total of 13 (33%) of the 39 patients achieved partial responses. In this study, 21 patients with squamous cell carcinoma were enrolled, 12 patients achieved PR and the response rate was 57%. The biological mechanism responsible for the antitumor activity of nedaplatin against squamous cell carcinoma of the lung remains unknown. In the pharmacokinetic analysis, no significant differences were observed in responding patients with squamous cell carcinoma compared with non-responding others. However, nedaplatin also has a favorable antitumor activity against head and neck cancer and esophageal cancer, which also have a high frequency of squamous cell histology [19–22]. Although antitumor activity was evaluated only in elderly patients in this study, the development of this activity is worthwhile in the treatment of NSCLC with squamous cell histology. Furthermore, a translational study to identify the biological and/or genetic mechanism responsible for the antitumor activity of nedaplatin against squamous cell carcinoma is also warranted.

In conclusion, the recommended doses of nedaplatin for elderly patients with NSCLC were determined based on renal function, a dose of 100 mg/m^2 every 4 weeks was recommended for patients with a Ccr ≥60 mL/min, and a dose of 80 mg/m^2 every 4 weeks was recommended for patients with 40 ≤ Ccr < 60 mL/min. Nedaplatin can be safely administered to elderly patients with an acceptable level of toxicity and favorable antitumor activities against NSCLC, especially squamous cell carcinoma.

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Japanese-US Common-Arm Analysis of Paclitaxel Plus Carboplatin in Advanced Non–Small-Cell Lung Cancer: A Model for Assessing Population-Related Pharmacogenomics

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ABSTRACT

Purpose
To explore whether population-related pharmacogenomics contribute to differences in patient outcomes between clinical trials performed in Japan and the United States, given similar study designs, eligibility criteria, staging, and treatment regimens.

Methods
We prospectively designed and conducted three phase III trials (Four-Arm Cooperative Study, LC00-03, and S0003) in advanced-stage, non–small-cell lung cancer, each with a common arm of paclitaxel plus carboplatin. Genomic DNA was collected from patients in LC00-03 and S0003 who received paclitaxel (225 mg/m^2) and carboplatin (area under the concentration-time curve, 6). Genotypic variants of CYP3A4, CYP3A5, CYP2C8, NR1I2-206, ABCB1, ERCC1, and ERCC2 were analyzed by pyrosequencing or by PCR restriction fragment length polymorphism. Results were assessed by Cox model for survival and by logistic regression for response and toxicity.

Results
Clinical results were similar in the two Japanese trials, and were significantly different from the US trial, for survival, neutropenia, febrile neutropenia, and anemia. There was a significant difference between Japanese and US patients in genotypic distribution for *CYP3A4*1B* ($P = .01$), *CYP3A5*3C* ($P = .03$), *ERCC1* 118 ($P < .0001$), *ERCC2* K751Q ($P < .001$), and *CYP2C8* R139K ($P = .01$). Genotypic associations were observed between *CYP3A4*1B* for progression-free survival (hazard ratio [HR], 0.36; 95% CI, 0.14 to 0.94; $P = .04$) and ERCC2 K751Q for response (HR, 0.33; 95% CI, 0.13 to 0.83; $P = .02$). For grade 4 neutropenia, the HR for ABCB1 3425C→T was 1.84 (95% CI, 0.77 to 4.48; $P = .19$).

Conclusion
Differences in allelic distribution for genes involved in paclitaxel disposition or DNA repair were observed between Japanese and US patients. In an exploratory analysis, genotype-related associations with patient outcomes were observed for *CYP3A4*1B* and *ERCC2* K751Q. This common-arm approach facilitates the prospective study of population-related pharmacogenomics in which ethnic differences in antineoplastic drug disposition are anticipated.

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INTRODUCTION

Results may vary between different clinical trials that evaluate the same treatment regimen for many reasons, including trial design, eligibility criteria, patient characteristics, and subtle alterations in the treatment regimens themselves. An additional explanation for divergence of outcomes is host-related genetic differences associated with ethnicity, which is particularly pertinent when trials that are performed in different parts of the world are compared.

More than 10 years ago, the Southwest Oncology Group (SWOG) established a collaboration with Japanese investigators of lung cancer to provide a forum for exchange of research data, to facilitate standardization of clinical trial design and conduct, and to establish areas for joint collaboration.[1] We hypothesized that outcome differences between trials performed in Japan and the United States that evaluated similar treatment regimens in advanced-stage, non–small-cell lung cancer (NSCLC) could be explained by population-related

pharmacogenomics. To evaluate this possibility, we prospectively designed three phase III trials, (Four-Arm Cooperative Study [FACS], LC00-03, and S0003), each with similar patient eligibility criteria, staging, and treatment with a common arm of paclitaxel plus carboplatin. We have reported previously that, despite this effort at trial standardization, differences in clinical outcomes were observed in Japanese versus US patients treated on these studies.[2,3] Herein, we report the results of a clinical and pharmacogenomic analysis that involved patients from two of the three clinical trials (LC00-03 and S0003), and we report implications for additional studies by using this clinical research approach in which population-related differences in drug disposition are anticipated.

METHODS

Patients

The clinical trial methodology employed was prospective design of three separate-but-equal, randomized, phase III trials in advanced-stage NSCLC, each with its own comparator regimens but linked by a common treatment arm of paclitaxel plus carboplatin. In FACS, patients were randomly assigned to a standard treatment in Japan (irinotecan plus cisplatin) versus experimental arms of paclitaxel plus carboplatin, gemcitabine plus cisplatin, and vinorelbine plus cisplatin. LC00-03 compared paclitaxel plus carboplatin to the nonplatinum regimen of sequential vinorelbine plus gemcitabine followed by docetaxel, whereas patients on S0003 were randomly assigned to paclitaxel plus carboplatin with or without the hypoxic cytotoxin tirapazamine.

Clinical results for the three trials have been previously presented and published separately.[4-6] Common elements of eligibility criteria are summarized here. All patients had histologically or cytologically confirmed chemotherapy-naïve NSCLC with stage IV (ie, no brain metastases) or selected stage IIIB disease (ie, positive pleural or pericardial effusion or multiple ipsilateral lung nodules); measurable or assessable disease, performance status (PS) of 0 or 1; and adequate hematologic, hepatic, and renal function. All patients gave written informed consent in accordance with institutional regulations, and each protocol was approved by the respective institutional review boards; trials were conducted with adherence to the Helsinki Declaration.

Treatment Schedule, Dose Modifications, and Toxicity Assessment

Study elements of S0003, FACS and LC00-03 were designed to be as similar as possible: each study contained a common arm of paclitaxel plus carboplatin, which was repeated on a 21-day schedule. In all three studies, carboplatin was dosed at an area under the concentration-time curve (AUC) of 6.0 mg/mL/min on day 1. Paclitaxel was dosed at 225 mg/m^2 in S0003 and LC00-03 and at 200 mg/m^2 in FACS because of regulatory requirements for this study; in each study, paclitaxel was delivered as a 3-hour infusion on day 1. Premedication to prevent paclitaxel-related allergic reactions were similar. Prophylactic granulocyte colony-stimulating factor was not utilized. A complete blood count and chemistries were performed on day 1 of each cycle. Dose modifications occurred as previously described.[4] Patients were evaluated every two cycles for objective response by using RECIST (Response Evaluation Criteria in Solid Tumors) criteria[7] Toxicity grading was performed in accordance with the National Cancer Institute Common Toxicity Criteria, version 2.0, in each study.[8]

DNA Extraction and Genotyping

Specimens were not available from FACS; therefore, this analysis compares pharmacogenomic results from LC00-03 with S0003. Whole-blood specimens were collected from consenting patients at the time of enrollment on to LC00-03 and S0003. For S0003, DNA was extracted from patient plasma by using the Gentra PureGene Blood Kit (Gentra, Minneapolis, MN) and the QIAamp DNA Blood midi kit (Qiagen, Valencia, CA), and DNA was reconstituted in a buffer that contained 10 mmol/L Tris (pH 7.6) and 1 mmol/L EDTA, as previously described.[9] For LC00-03, DNA was extracted from buffy coats by using the GenElute Blood Genomic DNA Kit (Sigma-Aldrich, St Louis, MO). Selected genotypic variants related to paclitaxel disposition (ie, the ABC transporter superfamily [multidrug resistance {MDR} transporter 1 P-glycoprotein, *ABCB1* 3435C→T], the pregnane X receptor (PXR, NR1I2-206 deletion), *CYP3A4* (*CYP3A4*1B* 392A→G, 5′ untranslated region), CYP3A5 (*CYP3A5*3C* 6986A→G, splice variant), *CYP2C8* (*CYP2C8*3* 416G→A, R139K) or to platinum-related DNA repair enzymes *ERCC1* (118C→T, silent) and ERCC2 (XPD, K751Q) previously reported to be of functional consequence were analyzed by polymerase chain reaction (PCR) or pyrosequencing, as previously described.[9-13] Briefly, PCR was conducted by using Amplitaq Gold PCR master mix (ABI, Foster City, CA), 5 pmol of each primer, and 5 to 10 ng of DNA. Pharmacogenetic analysis was conducted by using the Pyrosequencing hsAPSQ96 instrument and software (Biotage, Uppsala, Sweden). The genotype was considered variant if it differed from the Reference Sequence consensus sequence for the single-nucleotide polymorphism (SNP) position (http://www.ncbi.nlm.nih.gov/RefSeq/). The *ERCC1* polymorphism was analyzed by PCR restriction fragment length polymorphism, as previously described.[14]

Statistical Methods

Comparison of clinical results among the three trials was prospectively planned and was coordinated through the SWOG statistical center. Pharmacogenomic results were assessed by Cox model for progression-free survival (PFS) and overall survival and by logistic regression for response and toxicity, adjusted for sex and histology.[15] Comparisons of patient demographics, toxicity, and efficacy parameters were made, when applicable, from the available data sets, by two-sample *t* tests, log-rank tests, and Wilcoxon rank sum tests.

RESULTS

Clinical Results Summary

Clinical results are presented for all three trials to document similarities between the two Japanese trials compared with the US S003 trial, whereas pharmacogenomic information was derived only from LC00-03 and S0003. Table 1 summarizes characteristics of patients on the paclitaxel-plus-carboplatin arms of each of the three trials. The median ages and age ranges were similar, and there were no significant differences in sex, stage, or histology. In S0003, 3% of patients self-reported Asian heritage, not additionally specified. Toxicity, efficacy, and dose delivery comparisons are listed in Table 2, which compares S0003 versus FACS/LC00-03 when applicable. Grades 3 to 4 neutropenia and febrile neutropenia were comparable

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Trial: FACS (n = 145) No.	%	LC00-03 (n = 197) No.	%	S0003 (n = 184) No.	%	*P*
Age, years							.03*
Median	63		65		63		
Range	33-74		33-81		28-80		
Female sex	46	32	61	31	68	37	.42
Disease stage IV	117	81	162	82	161	87	.20
Nonsquamous tumor type	114	79	167	85	152	83	.17

Abbreviation: FACS, four-arm cooperative study.
*Two-sample *t* test to compare LC00-03 and S0003 data. Patient-level data not available for FACS.

Table 2. Toxicity Comparisons

Toxicity	Trial: FACS (n = 148) No.	FACS %	LC00-03 (n = 197) No.	LC00-03 %	S0003 (n = 184) No.	S0003 %	*P*
Neutropenia grades 3-4	130	88	137	70	70	38	< .0001
Febrile neutropenia grades 3-4	27	18	24	12	4	2	< .0001
Thrombocytopenia grades 3-4	16	11	14	7	12	6.5	.31
Anemia grades 3-4	22	15	16	8	12	7	.03
Neuropathy grades 2-4	25	17	32	16	30	16	.99

Abbreviation: FACS, four-arm cooperative study.

in FACS and LC00-03 and were significantly greater than in S0003. Anemia was more frequent in FACS compared with the two other trials (Table 2). Efficacy comparisons are summarized in Table 3. Response rates were similar between the three trials and ranged from 32% to 36%. Median PFS rates were 4.5, 6, and 4 months in FACS, LC00-03, and S0003, respectively. Median survival rates were higher in the Japanese studies at 12 and 14 months, versus 9 months in S0003, and 1-year survival was significantly higher in FACS and LC00-03 than in S0003 ($P = .0004$). Dose delivery, summarized in Table 4, was lower in FACS than in S0003 and LC00-03. Dose reductions were similar between LC00-03 and S0003. Dose reduction data were not available from FACS.

Pharmacogenomic Results

Table 5 lists allelic distributions of patients with common, heterozygous, and variant alleles in the Japanese (LC00-03) and US (S0003) trials. Fisher's exact test was used to determine whether allele distributions were different between the populations. There were significant differences between patients from Japan (LC00-03) and the United States (S0003) in genotype distribution for *CYP3A4*1B* ($P = .01$), *CYP3A5*3C* ($P = .03$), *ERCC1* 118 ($P < .0001$), *ERCC2* K751Q ($P < .001$), and *CYP2C8*3* ($P = .01$).

Across populations, genotypic correlations were observed between *CYP3A4*1B* for PFS (hazard ratio [HR], 0.36; 95% CI, 0.14 to 0.94; $P = .04$) and *ERCC2* K751Q for response (HR, 0.33; 95% CI, 0.13 to 0.83; $P = .02$). There were no other significant associations noted (Table 6). For grade 4 neutropenia, the HR for ABCB1 3425C→T was 1.84 (95% CI, 0.77 to 4.48; $P = .19$). The relationship between the ERCC2 polymorphism and patient response stems principally from US patients. All but one Japanese patient was homozygous for the common allele (A/A). Those who harbored one or more variant alleles were significantly more likely to respond to treatment compared with those who had the common genotype. The response rate for patients with variant alleles was 51% versus 19% for patients homozygous for the common allele $P = .004$). However, no differences were observed in overall survival when stratified by this locus.

In S0003 (ie, the US trial), there were seven African American patients who had specimens available for genotyping. African American patients accounted for all seven patients who were heterozygous or homozygous for the *CYP3A4*1B* allele (Table 5). Additionally, the three patients with the common allele for *CYP3A5*C* were African American.

Table 3. Efficacy Comparisons

Parameter	Trial: FACS (n = 145)	LC00-03 (n = 197)	S0003 (n = 184)	*P*
Response				.55
No.	47	73	61	
%	32	37	33	
PFS, months	4.5	6	4	.04*
MST, months	12	14	9	.0006*
1-year survival	51%	57%	37%	.0004

Abbreviations: FACS, four-arm cooperative study; PFS, progression-free survival; MST, median survival time.
*Log-rank test to compare LC00-03 and S0003. Patient-level data not available for FACS.

DISCUSSION

This report describes the culmination of a unique multinational and multistudy collaboration that explores the hypothesis that clinical differences in treatment outcomes between Japanese and US patients with NSCLC may be explained, in part, by pharmacogenomic factors. Potential differences in drug disposition related to ethnic variability in distribution of relevant single nucleotide polymorphisms are well recognized. To our knowledge, however, the current project represents the first attempt to prospectively incorporate study of this topic into a joint clinical trial design. To preplan such a multinational endeavor required a high level of collaboration and compromise among all participants, including, in the case of FACS, Japanese regulatory authorities. Nevertheless, this report demonstrates the overall feasibility of using a common-arm methodology to investigate this research topic, in which a single, prospectively planned, joint study cannot be conducted. Considering the limitations of the clinical and pharmacogenomic data sets generated in this effort, and considering the multiple comparisons generated, the results reported here should be viewed as exploratory only and as primarily useful for refining this common-arm model of multinational collaboration. Even so, the clinical results are remarkably consistent with those anticipated, in which expectations were for both improved efficacy and higher levels of toxicity in Japanese patients who received a similar treatment regimen. Observation of clinical differences despite reduced paclitaxel

Table 4. Treatment Delivered

Treatment Data	Trial						
	FACS (n = 145)		LC00-03 (n = 197)		S0003 (n = 184)		
	No.	%	No.	%	No.	%	*P*
Median cycles delivered	3.5		4		4		.07
Received > three cycles	35	24	118	60	100	54	< .0001
Received six cycles	16	11	58	29	68	36.5	< .0001
Dose was reduced	No data	No data	100	51	98	26	.63*

Abbreviation: FACS, four-arm cooperative study.
*Wilcoxon rank sum test to compare LC00-03 and S0003. Patient-level data not available for FACS.

dosing and drug delivery of paclitaxel plus carboplatin in the FACS Japanese study highlights the contrast.

The rationale for conducting this common-arm project specifically in collaboration with Japanese investigators was based on several factors, including the established SWOG interaction described earlier, the high quality of lung cancer investigation by Japanese cooperative groups, and prior literature that suggested that overall, Japanese patients achieve better results than their US counterparts. However, the most compelling rationale was prior pharmacogenomic literature, which suggested that relevant drug disposition differences might exist between US and Japanese populations treated with cancer chemotherapeutic agents. Well recognized here are alterations in irinotecan metabolism as a result of variability in the allelic distribution of UDP-glucuronosyltransferases, particularly *UGT1A1*28* in different ethnic groups, as Asians have a much lower frequency of variant alleles. Recently, a comparative analysis of patient-level data from phase III trials in small-cell lung cancer in Japan (J9511) and the United States (S0124) demonstrated significant differences in toxicity profiles between the two groups. In addition, a pharmacogenomic analysis of S0124 showed significant associations between genotypic variants and toxicity levels.[16,17]

Table 5. Genotype Profiles in Japanese and US Patients on LC00-03 and S0003

Polymorphism by Trial Location	No. of Patients			*P*
	Com	Het	Var	
*CYP3A4*1B*				
Japan	73	0	0	.01
United States	64	4	3	
*CYP3A5*C*				
Japan	7	16	50	.03
United States	3	7	66	
CYP2C8 (R139K)				
Japan	69	2	0	.01
United States	57	7	5	
ABCB1 (3435C→T)				
Japan	33	21	17	.11
United States	24	23	29	
NR1I2 (206 deletion)				
Japan	51	19	5	.25
United States	40	25	8	
ERCC1 (118)				
Japan	8	27	43	< .0001
United States	23	33	19	
ERCC2 (K751Q)				
Japan	73	1	0	< .001
United States	37	27	8	

NOTE. LC00-03 is the trial in Japan; S0003 is the trial in the United States. Fisher's exact test was used to determine whether allele distributions were different between the populations.
Abbreviations: Com, common allele; Het, heterozygous allele; Var, variant allele.

The genes evaluated in this study were selected on the basis of their potential to influence paclitaxel disposition or DNA damage repair. Paclitaxel is principally eliminated through multiple hydroxylation reactions mediated by cytochrome isoforms *CYP2C8, CYP3A4,* and *CYP3A5.*[18,19] The *CYP2C8*3* variant (R139K), which is associated with decreased metabolism of paclitaxel, occurs at a frequency of 9% to 15% in white patients but is rare in African and Asian populations.[20-23] In this study, the allele frequency in the US population was 12%, which was significantly different from the less-than-1% frequency in the Japanese cohort (P = .01). *CYP2C8* genotypic variability at R139K was not significantly associated with patient outcome. CYP3A isozymes account for 45% to 60% of paclitaxel metabolism.[24] In white patients, the *CYP3A5* allele is commonly nonfunctional as a result of a transition in intron 3 that produces a truncated splice variant.[25] Our findings are consistent with that of Hustert et al,[25] who reported frequencies of functional *CYP3A5* as 5% in white patients, 29% in Japanese patients, and 73% in African American patients. Of patients enrolled onto the S0003 trial conducted in the US, three of three with the functional allele (indicated as common in Table 5) were African Americans, as were three of the seven heterozygous patients. Although trends were observed, *CYP3A5*3C* genotypic variability was not significantly associated with patient outcome (overall survival *P* = .07; PFS *P* = .09), perhaps related to the small sample size. Similarly, the *CYP3A4*1B* allele was observed in seven of seven African American patients but was absent in white and Japanese patients. In vitro studies suggest that the *CYP3A4*1B* variant has enhanced activity over common allele.[26] An association was observed between occurrence of the *CYP3A4*1B* and PFS (*P* = .04); however, this association should be interpreted in the context that only African American patients harbored this allele. Thus, it remains unclear whether this potential relationship with outcome is associative or causative. The PXR (*NR1I2*-206 deletion) is a master regulator of genes involved in xenobiotic detoxification and influences transcription of *CYP3A4, CYP3A5, CYP2C8,* and *MDR-1 (ABCB1).*[27-29] Paclitaxel can activate PXR, which enhances drug clearance through increased activity of MDR1.[30] No significant differences by genotype were observed for PXR or ABCB1, although there was a trend toward

Table 6. Cox Model to Compare Outcomes by Polymorphism

Outcome by Polymorphism	Analyses			
	Comparison	HR	95% CI	*P*
ABCB1 3425				
Overall survival	Com *v* Het/Var (CC *v* CT/TT)	1.09	0.71 to 1.67	.69
PFS		1.04	0.70 to 1.56	.82
Response		0.97	0.39 to 2.38	1.00
Neutropenia		0.54	0.22 to 1.30	.19
CYP2C8 R139K				
Overall survival	Com *v* Het/Var (GG *v* GA/AA)	1.09	0.61 to 1.96	.76
PFS		1.12	0.63 to 2.00	.69
Response		1.92	0.46 to 11.11	.51
Neutropenia		1.30	0.35 to 5.00	.87
*CYP3A4*1B*				
Overall survival	Com *v* Het/Var (AA *v* AG/GG)	0.74	0.32 to 1.72	.48
PFS		0.36	0.14 to 0.94	.04
Response		0.63	0.10 to 4.76	.84
Neutropenia		0.44	0.04 to 2.94	.58
*CYP3A5*3C*				
Overall survival	Com/Het *v* Var (AA/AG *v* GG)	1.64	0.95 to 2.86	.07
PFS		1.56	0.93 to 2.63	.09
Response		1.61	0.53 to 4.76	.47
Neutropenia		1.30	0.44 to 3.85	.78
ERCC1 (118)				
Overall survival	TT *v* TC/CC	1.20	0.74 to 1.96	.45
PFS		1.11	0.69 to 1.82	.65
Response		1.45	0.48 to 4.17	.61
Neutropenia		0.57	0.20 to 1.61	.35
ERCC2 K751Q				
Overall survival	Com *v* Het/Var (AA *v* AC/CC)	0.97	0.63 to 1.49	.89
PFS		0.85	0.55 to 1.30	.45
Response		0.33	0.13 to 0.83	.02
Neutropenia		0.75	0.30 to 1.85	.63
nr1I2-206 del				
Overall survival	Com *v* Het/Var 206 deletion	0.82	0.53 to 1.25	.35
PFS		0.93	0.63 to 1.39	.75
Response		0.82	0.34 to 2.00	.77
Neutropenia		0.88	0.37 to 2.08	.90

Abbreviations: HR, hazard ratio; PFS, progression-free survival; Com, common allele; Het, heterozygous allele; Var, variant allele.

neutropenia ($P = .19$) for patients who harbored the ABCB1 3435 common allele.

The *ERCC2* gene, also known as xeroderma pigmentosum complementation group D, encodes a DNA helicase which complexes with TFIIH, a transcription factor essential for replication and nucleotide excision repair.[31] Several nonsynonymous SNPs have been described in this gene, including an Asp→Asn (G→A) at codon 312 in exon 10 and a Lys→Gln (A→C) at codon 751 in exon 23 and are likely in linkage disequilibrium with each other.[32,33] The functional consequences of these SNPs are still in contention, and the majority of studies indicate that variants in these alleles result in reduced DNA repair capacity.[34-41] Additionally, most studies indicate that *ERCC2* variants confer an increased risk of lung cancer.[32,34,35,42-48] In this study, 51% of patients (ie, 37 of 72 patients) from the US were homozygous wild type for the common (A) allele. These patients were significantly less likely to respond to treatment compared with US patients who had one or more variant alleles (A/C or C/C). However, no differences in overall survival were observed on the basis of *ERCC2* K751Q allele frequencies. In addition, this allele cannot account for the improved survival experienced by Japanese patients, as they uniformly harbored the common A/A genotype (and only one patient harbored A/C). The *ERCC1* 118 C→T SNP does not result in an amino acid substitution, although studies have nevertheless identified associations with patient outcome in various tumor types.[49] It has been suggested that this variant may modulate *ERCC1* mRNA and protein expression and/or may be in linkage disequilibrium with other functional SNPs.[14,50,51] However, three reports in NSCLC found no associations between the *ERCC1* 118 and patient outcome.[52-54] Here, we found a highly significant divergence in allele frequency between Japanese and US patients ($P < .0001$); however, no impact on patient outcome was observed.

In summary, the results of cancer clinical trials to test the same regimen may differ for a variety of reasons, including differences related to ethnicity. FACS, LC00-03, and S0003 were prospectively designed to facilitate a comparison of patient outcomes and pharmacogenomic results, in a setting where joint clinical trials sponsored by the US National Cancer Institute were not possible. Our

results suggest that global clinical trials (ie, those conducted internationally) should be carefully designed and conducted to account for potential genetic differences in the patient populations studied. This common-arm approach provides a model for the prospective study of population-related pharmacogenomics in which ethnic differences in antineoplastic drug disposition are anticipated.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

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ABSTRACT

BACKGROUND

Previous, uncontrolled studies have suggested that first-line treatment with gefitinib would be efficacious in selected patients with non–small-cell lung cancer.

METHODS

In this phase 3, open-label study, we randomly assigned previously untreated patients in East Asia who had advanced pulmonary adenocarcinoma and who were nonsmokers or former light smokers to receive gefitinib (250 mg per day) (609 patients) or carboplatin (at a dose calculated to produce an area under the curve of 5 or 6 mg per milliliter per minute) plus paclitaxel (200 mg per square meter of body-surface area) (608 patients). The primary end point was progression-free survival.

RESULTS

The 12-month rates of progression-free survival were 24.9% with gefitinib and 6.7% with carboplatin–paclitaxel. The study met its primary objective of showing the noninferiority of gefitinib and also showed its superiority, as compared with carboplatin–paclitaxel, with respect to progression-free survival in the intention-to-treat population (hazard ratio for progression or death, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). In the subgroup of 261 patients who were positive for the epidermal growth factor receptor gene (*EGFR*) mutation, progression-free survival was significantly longer among those who received gefitinib than among those who received carboplatin–paclitaxel (hazard ratio for progression or death, 0.48; 95% CI, 0.36 to 0.64; P<0.001), whereas in the subgroup of 176 patients who were negative for the mutation, progression-free survival was significantly longer among those who received carboplatin–paclitaxel (hazard ratio for progression or death with gefitinib, 2.85; 95% CI, 2.05 to 3.98; P<0.001). The most common adverse events were rash or acne (in 66.2% of patients) and diarrhea (46.6%) in the gefitinib group and neurotoxic effects (69.9%), neutropenia (67.1%), and alopecia (58.4%) in the carboplatin–paclitaxel group.

CONCLUSIONS

Gefitinib is superior to carboplatin–paclitaxel as an initial treatment for pulmonary adenocarcinoma among nonsmokers or former light smokers in East Asia. The presence in the tumor of a mutation of the *EGFR* gene is a strong predictor of a better outcome with gefitinib. (ClinicalTrials.gov number, NCT00322452.)

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Inhibitors of the epidermal growth factor receptor (EGFR) tyrosine kinase have clinical efficacy, as compared with the best supportive care[1] or standard chemotherapy,[2] when given as second-line or third-line therapy for advanced non–small-cell lung cancer. Treatment with EGFR tyrosine kinase inhibitors is most effective in women, patients who have never smoked, patients with pulmonary adenocarcinomas, and patients of Asian origin. In these populations, such treatment is associated with favorable rates of objective responses, progression-free survival, and overall survival.[1,3,4] These populations also have a relatively high incidence of somatic mutations in the region of the *EGFR* gene that encodes the tyrosine kinase domain.[5,6] Studies have shown that in patients with pulmonary adenocarcinoma who had a base-pair deletion at exon 19 (del746_A750) or a point mutation at exon 21 (L858R), the tumors were highly responsive to EGFR tyrosine kinase inhibitors,[7-9] and subsequent studies of first-line therapy with these agents showed objective response rates of 54.8 to 81.6% and progression-free survival of 9.7 to 13.3 months among patients with these mutations.[10-12]

On the basis of these and other studies,[1,4,13-16] we hypothesized that in a selected population, first-line therapy with an oral EGFR tyrosine kinase inhibitor would be at least as effective as chemotherapy with carboplatin–paclitaxel. In this study, we compared the efficacy, safety, and adverse-event profile of gefitinib with those of carboplatin–paclitaxel when these drugs were used as first-line treatment in nonsmokers or former light smokers in East Asia who had adenocarcinoma of the lung. We also examined the role of an *EGFR* mutation as a predicator of the efficacy of gefitinib or carboplatin–paclitaxel.

METHODS

STUDY DESIGN AND PATIENTS

The First Line Iressa versus Carboplatin/Paclitaxel in Asia (Iressa Pan-Asia Study [IPASS]) study was a phase 3, multicenter, randomized, open-label, parallel-group study comparing gefitinib (Iressa, AstraZeneca) with carboplatin (Paraplatin, Bristol-Myers Squibb) plus paclitaxel (Taxol, Bristol-Myers Squibb) as first-line treatment in clinically selected patients in East Asia who had advanced non–small-cell lung cancer. The primary end point was progression-free survival. Secondary end points included overall survival (an early analysis, since follow-up is ongoing), the objective response rate, quality of life, reduction in symptoms, safety, and the adverse-event profile. Evaluations of efficacy according to the baseline biomarker status of EGFR were planned exploratory objectives.

Patients were eligible for inclusion in the study if they were 18 years of age or older, had histologically or cytologically confirmed stage IIIB or IV non–small-cell lung cancer with histologic features of adenocarcinoma (including bronchoalveolar carcinoma), were nonsmokers (defined as patients who had smoked <100 cigarettes in their lifetime) or former light smokers (those who had stopped smoking at least 15 years previously and had a total of ≤10 pack-years of smoking), and had had no previous chemotherapy or biologic or immunologic therapy. Other eligibility criteria are described in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The principal investigators and the members of the steering committee (see the Appendix at the end of this article) designed the study in collaboration with the sponsor (AstraZeneca) and supervised the conduct of the trial. The sponsor collected and analyzed the data. The lead academic author had unrestricted access to the data and vouches for the validity and completeness of the results of the trial (see the Supplementary Appendix for further details). All patients provided written informed consent; separate consent was provided for the assessment of EGFR biomarkers. 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 Harmonization Guidelines for Good Clinical Practice, applicable regulatory requirements, and AstraZeneca's policy on bioethics. One planned interim analysis was performed by an independent statistician and reviewed by an independent data and safety monitoring committee (see the Supplementary Appendix).

STUDY TREATMENT

Patients were randomly assigned, in a 1:1 ratio, to receive gefitinib (250 mg per day, administered orally) or paclitaxel (200 mg per square meter of body-surface area, administered intravenously over a 3-hour period on the first day of the cycle) fol-

lowed immediately by carboplatin (at a dose calculated to produce an area under the concentration–time curve of 5.0 or 6.0 mg per milliliter per minute, administered intravenously over a period of 15 to 60 minutes) in cycles of once every 3 weeks for up to 6 cycles. Randomization was performed with the use of dynamic balancing[17] with respect to performance status, as assessed by the World Health Organization (WHO) performance scale measuring activity (0 or 1, or 2 on a scale of 0 to 4, with lower numbers indicating a higher degree of activity); smoking status (nonsmoker or former light smoker); sex; and center. Treatment continued until progression of the disease, development of unacceptable toxic effects, a request by the patient or physician to discontinue treatment, serious noncompliance with the protocol, or completion of six chemotherapy cycles. Among patients assigned to gefitinib therapy, those whose tumor progressed were offered the opportunity to switch to treatment with carboplatin–paclitaxel; however, if the patient declined or was not a good candidate for that treatment, he or she could receive another approved therapy of the physician's choice. Among patients who were receiving carboplatin–paclitaxel, further therapy after progression of the disease was at the physician's discretion.

ASSESSMENTS

Progression-free survival was assessed from the date of randomization to the earliest sign of disease progression, as determined by means of the Response Evaluation Criteria in Solid Tumors (RECIST),[18] or death from any cause. Overall survival was assessed from the date of randomization until death from any cause. Tumor response was assessed every 6 weeks until disease progression. Quality of life was assessed with the use of the Functional Assessment of Cancer Therapy–Lung (FACT–L) questionnaire (in which scores range from 0 to 136, with higher scores indicating better quality of life) and the Trial Outcome Index (TOI, which is the sum of the physical well-being, functional well-being, and lung-cancer subscale [LCS] scores of FACT-L; scores range from 0 to 84, with higher scores indicating better quality of life), and symptoms were assessed with the use of the LCS score (scores range from 0 to 28, with higher scores indicating fewer symptoms). The FACT-L questionnaire[19] was administered at randomization and at week 1, once every 3 weeks until day 127, once every 6 weeks from day 128 until disease progression, and when the study drug was discontinued. Clinically relevant improvement was predefined as an improvement of six points or more in FACT-L and TOI scores or an improvement of two points or more in LCS scores, with the higher scores maintained for at least 21 days.[20] Safety and tolerability were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Tumor samples from patients who consented to have biomarkers assessed were analyzed at two central laboratories to determine biomarker status, with *EGFR* mutation status the first priority. Patients were considered to be positive for the *EGFR* mutation if 1 of 29 *EGFR* mutations was detected with the use of the amplification refractory mutation system (ARMS) and the DxS EGFR29 mutation-detection kit.[21,22]

STATISTICAL ANALYSIS

The primary end point (progression-free survival) was analyzed with the use of a Cox proportional-hazards model in the intention-to-treat population (all randomly assigned patients) to assess the noninferiority of gefitinib as compared with carboplatin–paclitaxel, with the WHO performance status (0 or 1, or 2), smoking status (nonsmoker or former light smoker), and sex as covariates. For noninferiority to be demonstrated, the 95% confidence interval for the hazard ratio had to lie entirely below the predefined noninferiority limit of 1.2. We estimated that with a total of 944 progression events, the study would have 80% power to demonstrate noninferiority if the treatments were truly equal, with a two-sided 5% probability of an erroneous demonstration of noninferiority. If the 95% confidence interval for the hazard ratio was also below 1, the P value would be less than 0.05 and superiority could be concluded from the same analysis without statistical penalty (closed test procedure).[23] Supportive secondary analyses are described in the Supplementary Appendix. Planned subgroup analyses were performed to compare progression-free survival between treatments in groups defined according to WHO performance status (0 or 1, or 2), smoking status (nonsmoker or former light smoker), sex, age at randomization (<65 years or ≥65 years), disease stage at screening (stage IIIB or IV), and presence or absence of biomarkers. Tests to determine in-