count 4000–12 000 μl^{-1}, haemoglobin concentration $\geqslant$9.5 g dl^{-1} platelet count $\geqslant$100 000 μl^{-1}), kidney function (creatinine $\leqslant$ upper limit of normal, 24-h creatinine clearance $\geqslant$60 ml min^{-1}), liver function (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leqslant$2.0 times the upper limit of normal, total bilirubin $\leqslant$1.5 mg dl^{-1}), and pulmonary function ($PaO_2 \geqslant 60$ torr). Patients with active concomitant or a recent (<3 years) history of any malignancy, symptomatic brain metastases, past history of drug allergy reactions, complication by interstitial pneumonia, watery diarrhoea, ileus, treatment with nonsteroidal anti-inflammatory drugs, or other serious complications, such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus or hypertension, massive pleural effusion or ascites, or serious active infection were excluded. All patients gave written informed consent, and the institutional review board for human experimentation approved the protocol.

Study evaluations

Pretreatment studies included a complete medical history and physical examination, chest X-ray, electrocardiography, computed tomography (CT) scan of the brain and chest, CT or ultrasound examination of the abdomen, and bone scintigraphy. Blood and blood chemistry studies included complete blood cell count, liver function test, serum electrolytes, serum creatinine, and blood urea nitrogen. Chest X-ray, blood and blood chemistry analyses, and urinalysis were repeated weekly.

Randomisation and treatment schedule

Patients were randomly assigned to receive the DC regimen or the DI regimen by a minimisation method using stage (IIIB/IV) and treatment institution. The DC regimen was consisting of docetaxel 60 mg m^{-2} on day 1 and cisplatin 80 mg m^{-2} on day 1, and the DI regimen was consisting of docetaxel 60 mg m^{-2} as a 60-min intravenous infusion on day 8 and irinotecan 60 mg m^{-2} as a 90-min intravenous infusion on days 1 and 8 (Figure 1). Both regimens were repeated every 3 weeks. Participating researchers at each institution decided the amount of fluid replacement and the type of antiemetic therapy to administer. Standard antiemetic treatment in the DC arm consisted of 5-HT_3 receptor antagonist plus 16 mg dexamethasone intravenously on day 1, before cisplatin administration. In the DI arm, standard antiemetic treatment consisted of 5-HT_3 receptor antagonist intravenously before chemotherapy administration on days 1 and 8. Patients received at least two treatment cycles, and those with a complete or partial response after two cycles had treatment continued until there was evidence of disease progression, intolerable toxicity, or patient refusal.

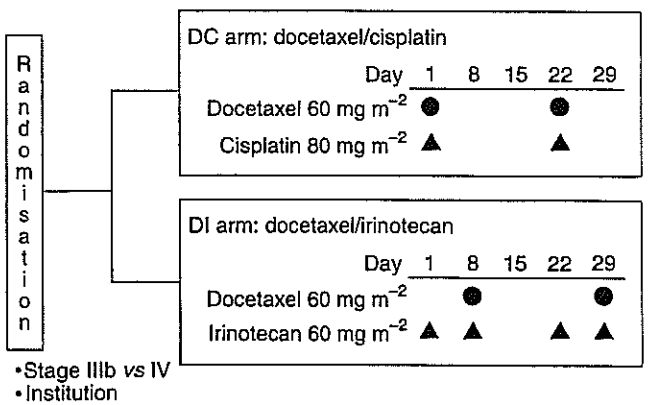

Figure 1 *Treatment schema*: after stratification by stage and institution, enrolled patients were randomly allocated to receive docetaxel plus cisplatin (DC) or docetaxel plus irinotecan (DI).

Dose modifications

Toxicity assessment was based on the National Cancer Institute–Common Toxicity Criteria version 2.0. Dose levels and treatment schedule were modified to avoid severe adverse effects. Patients receiving DI had the day-8 docetaxel and irinotecan doses postponed to day 15 if any of the following toxicities was present on day 8: leucocyte count <3000 μl^{-1}, platelet count <100 000 μl^{-1} diarrhoea consisting of bloody or watery stools, or increased to two or more diarrhoea within 24 h, abdominal pain rated mild or worse, hepatic toxicity $\geqslant$grade 3, or fever >38°C. If these toxicities occurred on day 15 after skipping the day-8 treatment, DI was stopped in that course.

Patients could receive the next treatment course only if the following criteria were met: leucocyte count $\geqslant$4000 μl^{-1}, platelet count $\geqslant$100 000 μl^{-1} AST/ALT <2.0 times the upper limit of normal, total bilirubin $\leqslant$1.5 mg dl^{-1} serum creatinine $\leqslant$ the upper limit of normal, ECOG PS$\leqslant$2, neurotoxicity $\leqslant$grade 1, no diarrhoea or oedema. However, if more than 6 weeks passed before these criteria were satisfied, the patient was removed from the study.

Dose modification criteria for each drug are shown in Table 1. If during the previous course, grade 4 leucopenia, grade 4 neutropenia lasting $\geqslant$3 days, or grade 4 thrombocytopenia had occurred, doses of all drugs were reduced by 10 mg m^{-2}. Doses of both cisplatin and docetaxel were reduced by 10 mg m^{-2} in subsequent cycles if chemotherapy induced grade $\geqslant$2 neurotoxicity. Moreover, dose of docetaxel was reduced by 10 mg m^{-2} if grade $\geqslant$2 hepatic toxicity or grade $\geqslant$3 stomatitis had occurred. Dose of cisplatin was reduced by 20/mg/m^2 if grade $\geqslant$2 renal toxicity occurred. Dose of irinotecan was reduced by 5 mg m^{-2} if grade $\geqslant$2 hepatic toxicity had occurred and by 10 mg m^{-2} if grade $\geqslant$2 diarrhoea or cancellation of day-8 treatment had occurred.

Evaluation of response and survival

Tumour response was classified according to World Health Organization (WHO) criteria (World Health Organization, 1979). Complete response was defined as complete disappearance of all measurable and assessable disease for at least 4 weeks, Partial response was a $\geqslant$50% decrease in the sum of the products of the two IL largest perpendicular diameters of all measurable tumours lasting at least 4 weeks and without appearance of any new lesions. No change was defined as a <50% decrease or a <25% increase of tumor lesions for at least 4 weeks with no new lesions.

Table 1 Dose modification criteria

Toxicities in previous cycle	Decrease in docetaxel dose (mg/m^{-2})	Decrease in cisplatin dose (mg/m^{-2})	Decrease in -irinotecan dose (mg/m^{-2})
Grade 4 neutropenia lasting $\geqslant$3 days, leucopenia or thrombocytopenia	10	10	10
Grade $\geqslant$2 neurotoxicity	10	10	—
Grade $\geqslant$2 renal toxicity	—	20	—
Grade $\geqslant$2 hepatic toxicity	10	—	5
Grade $\geqslant$3 stomatitis	10	—	—
Grade $\geqslant$2 diarrhoea	—	—	10
Cancellation of day-8 treatment	—	—	10

Progressive disease was defined as development of new-lesions or a 25% increase in the sum of the products of the two largest perpendicular diameters of all measurable tumors. Duration of response in patients who achieved complete or partial response was measured from the start of treatment to the date of disease progression.

Statistical methods

Results of this study were evaluated to determine whether the docetaxel plus irinotecan combination warranted further assessment in a phase III trial. Thus, this study was designed to conduct two randomised phase II studies concurrently. We calculated the number of patients required for each of the two studies based on the Fleming's single-stage procedure (Fleming, 1982). In both studies, we set response rates of 40% as target activity level and 20% as the lowest level of interest with a power of 0.9 at a one-sided significance level of 0.05. As a result, a total of 100 qualified patients were to be enrolled, with 50 patients in each treatment arm. The primary objective was to estimate the response rate to both regimens, particularly to irinotecan plus docetaxel.

Overall survival and progression-free survival were analysed by the Kaplan–Meier method. The overall survival was measured from study entry to death. The progression-free survival was measured from study entry until the day of the first evidence of disease progression. If the disease had not progressed by the time of this analysis, progression-free survival was considered censored at the time of the analysis. All comparisons between patient characteristics, response rates, and toxicity incidences were performed by Pearson's χ^2 contingency table analysis.

RESULTS

Patient characteristics

From October 1998 to August 1999, 108 patients were assigned to receive DC ($n=51$) or DI ($n=57$). Baseline patient characteristics according to treatment arm are shown in Table 2. Patients were well balanced between the two treatment arms in terms of gender, age, performance status, disease stage, and histologic subtypes. There were 23% stage IIIb patients and 74% had adenocarcinoma. All patients were included in the survival evaluation, and all were assessable for antitumor efficacy and toxicity.

Treatment delivery

Patients in both treatment arms received a median of two treatment courses. Two or more courses were delivered to 72.5 and 71.9%, and four courses to 17.6 and 19.1% of patients in the DC and DI arms, respectively. Differences between arms in the number of chemotherapy courses administered were not statistically significant.

Table 2 Baseline patient characteristics

		Docetaxel/ cisplatin	Docetaxel/ irinotecan	χ^2 text
No. of patients		51	57	
Gender	Male/female	37/14	38/19	$P=0.537$
Age (years)	Median	62	60	
	Range	39–74	42–77	
PS	0/1	15/36	15/42	$P=0.830$
Histology	Adenocarcinoma	36	44	$P=0.520$
	Squamous cell carcinoma	13	9	
	Others	2	4	
Disease stage	IIIb/IV	11/40	14/43	$P=0.820$
Brain metastasis	(+)/(−)	4/47	11/46	$P=0.086$

PS = performance status.

Response to treatment and survival

There were no complete responses. In the DC arm, 19 patients had partial responses for an overall response rate of 37% (Table 3). Among DI patients, 18 had partial responses for an overall response rate of 32%. The difference in response rate between arms was not significant ($P=0.55$). Progressive disease was noted in twice as many DI (25%) than DC (12%) patients. Early deaths within 3 months of treatment initiation occurred in 10% ($n=5$) of DC and 5% ($n=3$) of DI patients. The early deaths were treatment-related (three patients, all in the DC arm) or due to disease progression (five patients).

Overall and progression-free survival curves for the two treatment arms are shown in Figures 2 and 3. The median progression-free survival time was 20 weeks (95% confidence interval: 14–25 weeks) in the DC arm *vs* 18 weeks (95% confidence interval: 12–22 weeks) in the DI arm. Median survival times, 1-year survival rates, and 2-year survival rates were 50 weeks (95% confidence interval 34–78 weeks), 47 and 25%, respectively, in the DC arm, and 46 weeks (95% confidence interval: 37–54 weeks), 40 and 18%, respectively, in the DI arm. No significant differences were noted between groups in progression-free survival ($P=0.33$) or overall survival ($P=0.50$), although there were trends toward higher 1-year and 2-year survival rates in the DC.

Table 3 Overall response to docetaxel/cisplatin (DC) or docetaxel/irinotecan (DI) in patients with stages IIIb/IV non-small-cell lung cancer

Response	DC ($n=51$) No. pts	DI ($n=67$) No. pts
Complete response	0	0
Partial response	19	18
No change	23	25
Progressive disease	6	14
NE (TRD)	3	0
Response rate	37.3%*	31.6%*
95% Confidence intervals	24.1–51.9%	19.9–45.2%

pts = patients; NE = not evaluable; TRD = treatment-related death. *$P=0.55$.

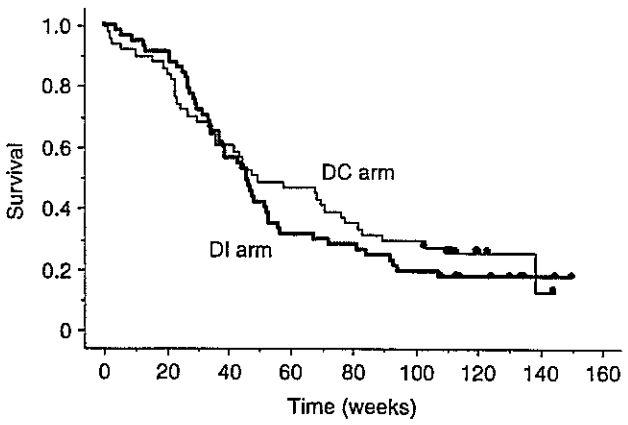

Figure 2 Overall survival according to treatment group, calculated by Kaplan–Meier method. Median survival times were 50 weeks for DC (docetaxel plus cisplatin) and 46 weeks for DI (docetaxel plus irinotecan). $P=0.50$ between treatment groups.

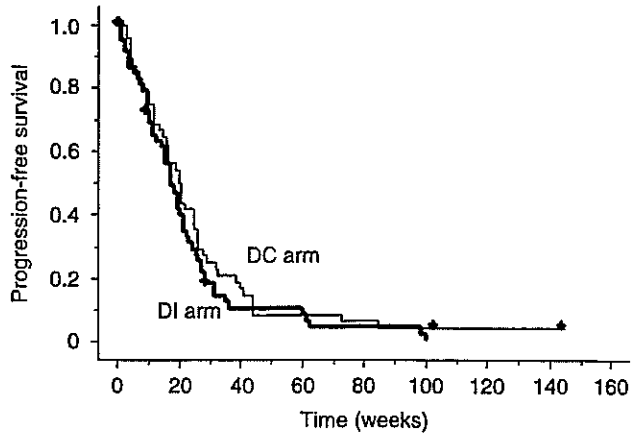

Figure 3 Progression-free survival according to treatment group, calculated by Kaplan–Meier method. Median progression-free survival times were 20 weeks for DC (docetaxel plus cisplatin) and 18 weeks for DI (docetaxel plus irinotecan). $P=0.33$ between treatment groups.

Table 4 Haematologic toxicity: maximum toxicity grade in any course

	Docetaxel/ cisplatin (% pts)			Docetaxel/ irinotecan (% pts)		
Toxicity/grade	**2**	**3**	**4**	**2**	**3**	**4**
Leucopenia*	31	43	4	26	40	16
Neutropenia*	10	31	43	4	23	61
Anaemia	47	10	2	46	7	0
Thrombocytopenia**	10	4	0	0	0	0
Febrile neutropenia		20			28	

pts = patients. *$P<0.01$ for grade 4; **$P<0.01$ for the sum of grades 2 and 3.

Second-line chemotherapy was administered to 61 patients (24 DC and 37 DI patients). A total of 22 patients in the DI group received cisplatin-based second-line chemotherapy and five had partial responses to this treatment (overall response rate, 23%). In particular, nine patients were subsequently treated with vinorelbine containing regimen and three patients had a partial response. Only two patients in the DC group received an irinotecan-containing regimen, one of whom had a partial response. Concerning as second-line chest irradiation, 8 patients in the DC group and 13 patients the DI group received.

Toxicity

Haematologic and nonhaematologic toxicities are listed in Tables 4 and 5. Grade 4 leucopenia and neutropenia occurred in a significantly higher percentage of DI than DC patients (leucopenia 16 *vs* 4%, $P<0.01$; neutropenia 61 *vs* 43%, $P<0.01$). On the other hand, there was a higher rate of grade $\geqslant 2$ thrombocytopenia in the DC than in the DI arm (14 *vs* 0%, $P<0.01$). Rates of anaemia (decrease in haemoglobin) and febrile neutropenia were similar in both groups.

Nonhaematologic toxicities including grade $\geqslant 2$ nausea (88 *vs* 51%, $P<0.01$), vomiting (39 *vs* 14%, $P<0.01$), and renal toxicity (increased serum creatinine; 12 *vs* 2%, $P<0.01$) were significantly more prevalent in the DC than in the DI arm, respectively. On the other hand, grade $\geqslant 2$ diarrhoea occurred significantly more often in DI than in DC patients (24 *vs* 42%, $P=0.01$). Other nonhaematologic toxicities, such as hepatic toxicity and peripheral neuropathy, were mild and occurred with similar frequency in both groups.

Table 5 Nonhaematologic toxicity: maximum toxicity grade in any course

	Docetaxel/ cisplatin (% pts)			Docetaxel/ irinotecan (% pts)		
Toxicity/grade	**2**	**3**	**4**	**2**	**3**	**4**
Diarrhoea*	18	6	0	26	12	4
Nausea*	53	33	0	33	18	0
Vomiting**	33	2	4	14	0	0
Peripheral neuropathy	2	0	0	2	0	0
AST increase	8	2	2	7	0	2
ALT increase	14	4	0	9	2	2
ALP increase	8	2	0	4	0	0
Creatinine increase*	10	0	2	0	0	2

pts = patients; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase. *$P<0.01$ for the sum of grades 2, 3, and 4; **$P=0.01$ for the sum of grades 2, 3, and 4.

There were three treatment-related deaths in the DC arm, which were due to febrile neutropenia and sepsis (one of these patients also developed perforation of the oesophagus). No treatment-related deaths occurred in the DI arm. The difference in incidence of treatment-related deaths was not significant.

DISCUSSION

Results of this randomised phase II study showed that the doublet chemotherapy regimens DC and DI had comparable activity in patients with advanced NSCLC. A primary goal of this study was to determine whether the DI combination should be studied in the phase III setting. Although there were no differences between DI and DC–a third-generation cisplatin-containing regimen–in overall and progression-free survival, patients who received DI tended to have lower 1-year and 2-year survival rates. Furthermore, overall toxicity was not reduced in the DI arm compared with the DC arm. Leucopenia and neutropenia were the major toxicities in both groups. As expected, emesis and renal toxicity were more prevalent in patients receiving DC, and diarrhoea occurred more frequently with DI.

Cisplatin has played a prominent role in the treatment of NSCLC, despite a relatively unimpressive single-agent response rate and a relatively severe toxicity profile. In 1995, the Non-Small Cell Lung Cancer Collaborative Group published a pivotal meta-analysis of chemotherapy in lung cancer and demonstrated the advantage of cisplatin-based regimens over best supportive care (Non-Small Cell Lung Cancer Collaborative Group, 1995). In the 1990s, third-generation chemotherapeutic agents, including paclitaxel, docetaxel, vinorelbine, gemcitabine and irinotecan, were shown to have higher response rates often coupled with fewer adverse effects (no renal toxicity, no massive dehydration, less emesis, etc.) than cisplatin. For example, single-agent paclitaxel (Ranson *et al*, 2000), docetaxel (Roszkowski *et al*, 2000), or vinorelbine (The Elderly Lung Cancer Vinorelbine Italian Study Group, 1999) significantly improved survival compared with best supportive care in patients with advanced NSCLC. Studies of single-agent gemcitabine (Perng *et al*, 1997) or irinotecan (Negoro *et al*, 2003) demonstrated a survival benefit comparable to that of second-generation chemotherapy regimens (cisplatin plus vindesine, cisplatin plus etoposide). Based on the above results, we thought that combination chemotherapy consisting of third-generation agents might improve outcome for patients with advanced NSCLC.

Only one published study compared cisplatin-based and noncisplatin-based regimens that included third-generation

agents. Georgoulias *et al* (2001) conducted a randomised study of cisplatin plus docetaxel (CD) *vs* gemcitabine plus docetaxel (GD) in 441 advanced NSCLC patients. The noncisplatin regimen provided a comparable response rate (CD 32.4%, GD 30.2%) and median survival time (CD 10 months, GD 9.5 months) but with less toxicity. The authors stated that the non-cisplatin GD regimen would likely be more acceptable to patients based on convenience of administration. However, several randomized trials reported at recent international meetings showed slightly shorter survival times with noncisplatin compared with cisplatin-based combinations. Preliminary results of the EORTC-Lung Cancer Group phase III study of cisplatin plus paclitaxel *vs* cisplatin plus gemcitabine *vs* paclitaxel plus gemcitabine in 480 patients with advanced NSCLC revealed superior overall survival and progression-free survival with the cisplatin-based regimens (Van Meerbeeck *et al*, 2001). Moreover, in a recent Italian–Canadian intergroup study of 501 patients comparing gemcitabine plus vinorelbine with cisplatin plus vinorelbine or gemcitabine, the noncisplatin regimen provided only short-term and sporadic advantages in some quality-of-life components, but there were no significant differences in overall and progression-free survival (Gridelli *et al*, 2002).

The best known noncisplatin platinum-based chemotherapy regimen is the paclitaxel plus carboplatin doublet. A Southwest Oncology Group study compared vinorelbine plus cisplatin with paclitaxel plus carboplatin. No differences in the overall survival or quality of life were noted between the two treatment groups, but toxicity rates were significantly lower in patients who received paclitaxel plus carboplatin (Chen *et al*, 2002). Results of a recent ECOG randomised phase III trial evaluating four platinum-based chemotherapy regimens showed no significant differences in the overall survival, while the paclitaxel plus carboplatin combination was less toxic than cisplatin-based chemotherapy (Schiller *et al*, 2002). Based on these findings, the paclitaxel plus carboplatin regimen is considered a standard therapy for previously untreated patients with advanced NSCLC, with activity comparable to that of cisplatin-based regimens and better tolerability.

The utility of doublet regimens containing third-generation chemotherapeutic agents for advanced NSCLC thus needs to be evaluated against the paclitaxel plus carboplatin combination, and several such studies were reported or are ongoing. The Hellenic Cooperative Oncology Group is conducting a phase III randomised study of paclitaxel plus carboplatin *vs* paclitaxel plus gemcitabine, and final results indicate comparable activity, toxicity and total cost of the two regimens in patients with inoperable NSCLC (Kosmidis *et al*, 2002). The Taiwan group conducted a similar study and found that paclitaxel plus carboplatin and paclitaxel plus gemcitabine had similar efficacy in the treatment of NSCLC, but that paclitaxel plus carboplatin was more cost-effective (Chen *et al*, 2002).

As mentioned in the introductory paragraphs, we conducted a phase I study of docetaxel plus irinotecan (DI) in patients with advanced NSCLC, and had a promising response rate of 48% and median survival time of 48 weeks (Masuda *et al*, 2000). Although we recommended docetaxel 50 mg m^{-2} on day 1 plus irinotecan 50 mg m^{-2} on days 1, 8, and 15 in the phase I study, more than half of patients could not receive irinotecan on day 15 because of haematologic toxicities. Accordingly, the day-15 irinotecan dose was omitted and the day-2 docetaxel dose moved to day 8 and increased from 50 to 60 mg m^{-2} in this randomised phase II trial.

It has been reported that second-line chemotherapy compared with best supportive care may increase the overall survival in patients with advanced NSCLC, and more studies in this regard are needed. In a recent study in which patients received cisplatin-based chemotherapy followed by docetaxel or supportive care alone, the median survival was significantly longer in the docetaxel-treated patients (Shepherd *et al*, 2000). In our study, 52% of patients were treated with second-line chemotherapy. Of these, 19 (33%) DI patients received cisplatin-based second-line chemotherapy, five of whom (26%) responded. Thus, cisplatin-based chemotherapy is capable of exerting antitumour activity in patients who have relapsed after having received noncisplatin-containing regimens.

Only two patients in the DC group received an irinotecan-containing regimen, one of whom had a partial response. As there were only two patients, we cannot judge whether irinotecan-containing regimen is effective for the patients after having received cisplatin-containing regimen.

In conclusion, docetaxel plus irinotecan combinations may be reasonable treatment options for NSCLC patients who cannot tolerate cisplatin. However, as there was no significant difference in the overall survival and no reduction in overall toxicity, DI has not improved on results obtained with DC. Thus, we will not select docetaxel/irinotecan as the experimental regimen in the next phase III study of first-line treatment of advanced NSCLC.

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Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan

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Background: To compare the efficacy and toxicity of three platinum-based combination regimens against cisplatin plus irinotecan (IP) in patients with untreated advanced non-small-cell lung cancer (NSCLC) by a non-inferiority design.
Patients and methods: A total of 602 patients were randomly assigned to one of four regimens: cisplatin 80 mg/m^2 on day 1 plus irinotecan 60 mg/m^2 on days 1, 8, 15 every 4 weeks (IP) carboplatin AUC 6.0 min × mg/mL (area under the concentration–time curve) on day 1 plus paclitaxel 200 mg/m^2 on day 1 every 3 weeks (TC); cisplatin 80 mg/m^2 on day 1 plus gemcitabine 1000 mg/m^2 on days 1, 8 every 3 weeks (GP); and cisplatin 80 mg/m^2 on day 1 plus vinorelbine 25 mg/m^2 on days 1, 8 every 3 weeks (NP).
Results: The response rate, median survival time, and 1-year survival rate were 31.0%, 13.9 months, 59.2%, respectively, in IP; 32.4%, 12.3 months, 51.0% in TC; 30.1%, 14.0 months, 59.6% in GP; and 33.1%, 11.4 months, 48.3% in NP. No statistically significant differences were found in response rate or overall survival, but the non-inferiority of none of the experimental regimens could be confirmed. All the four regimens were well tolerated.
Conclusion: The four regimens have similar efficacy and different toxicity profiles, and they can be used to treat advanced NSCLC patients.
Key words: carboplatin, cisplatin, gemcitabine, irinotecan, non-small-cell lung cancer, paclitaxel, randomized phase III study, vinorelbine

original article

introduction

Nearly 60 000 patients in Japan died of lung cancer in 2004, and the mortality rate is still increasing [1]. Even old-generation cisplatin-based chemotherapy provides a survival benefit and symptom relief in patients with inoperable non-small-cell lung cancer (NSCLC) [2]. Several anticancer agents including irinotecan, paclitaxel, docetaxel, gemcitabine, and vinorelbine, were developed in the 1990s and most of them have mechanisms of action that differ from those of the old-generation agents [3–7]. The combinations of platinum and these new agents developed in the 1990s are more useful against advanced NSCLC than old-generation combination chemotherapy, and doublets of platinum and new-generation anticancer agents are considered standard chemotherapy regimens for advanced NSCLC, although no consistent standard regimens have yet been established [8–17].

Two phase III studies comparing cisplatin plus irinotecan (IP) with cisplatin plus vindesine for advanced NSCLC have been conducted in Japan [18, 19]. Fukuoka et al. [20] reported the results of a combined analysis of the 358 eligible stage IV patients in these studies. They carried out a multivariate analysis using the Cox regression model with adjustment for well-known prognostic factors, and the Cox regression analysis demonstrated that treatment with IP was one of significant independent favorable factor. Based on their data, we selected IP for the reference arm in our study.

The Ministry of Health, Labour and Welfare of Japan approved the prescription of paclitaxel, gemcitabine, and

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vinorelbine for NSCLC in 1999 and requested a phase III study to confirm the efficacy and safety of these agents. The Japanese investigators and the pharmaceutical companies decided to conduct a four-arm randomized phase III study for NSCLC, the so-called FACS, Four-Arm Cooperative Study. The purpose of the study was to compare the efficacy and toxicity of three platinum-based combination regimens, carboplatin plus paclitaxel (TC), cisplatin plus gemcitabine (GP), cisplatin plus vinorelbine (NP), with IP as the reference arm.

patients and methods

patient selection

Patients with histologically and/or cytologically documented NSCLC were eligible for participation in the study. Each patient had to meet the following criteria: clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy, such as malignant pleural effusion, pleural dissemination, malignant pericardiac effusion, or metastatic lesion in the same lobe), at least one target lesion >2 cm, no prior chemotherapy, no prior surgery and/or radiotherapy for the primary site, age 20–74 years, Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, adequate hematological, hepatic and renal functions, partial pressure of arterial oxygen (paO_2) ≥60 torr, expected survival >3 months, able to undergo first course treatment in an inpatient setting, and written informed consent. The study was approved by the Institutional Review Board at each hospital. Written informed consent was obtained from every patient.

treatment schedule

All patients were randomly assigned to one of the four treatment groups by the central registration office by means of the minimization method. Stage, PS, gender, lactate dehydrogenase (LDH) and albumin values, and institution were used as adjustment variables. The first group received the reference treatment, 80 mg/m^2 of cisplatin on day 1 and 60 mg/m^2 of irinotecan on days 1, 8, and 15, and the cycle was repeated every 4 weeks. The second group received 200 mg/m^2 of paclitaxel (Bristol-Myers K.K., Tokyo, Japan) over a 3-h period followed by carboplatin at a dose calculated to produce an area under the concentration–time curve of 6.0 min × mg/mL on day 1 and the cycle was repeated every 3 weeks. The third group received 80 mg/m^2 of cisplatin on day 1 and 1000 mg/m^2 of gemcitabine (Eli Lilly Japan K.K., Kobe, Japan) on days 1, 8 and the cycle was repeated every 3 weeks. The fourth group received 80 mg/m^2 of cisplatin on day 1 and 25 mg/m^2 of vinorelbine (Kyowa Hakko Kogyo Co. Ltd., Tokyo, Japan) on days 1, 8 and the cycle was repeated every 3 weeks. Each treatment was repeated for three or more cycles unless the patient met the criteria for progressive disease or experienced unacceptable toxicity.

response and toxicity evaluation

Response was evaluated according to the Response Evaluation Criteria in Solid Tumors, and tumor markers were excluded from the criteria [21]. Objective tumor response in all responding patients was evaluated by an external review committee with no information on the treatment group. Toxicity grading criteria in National Cancer Institute Common Toxicity Criteria Ver 2.0 were used to evaluate toxicity.

quality of life assessment

Quality of life (QoL) was evaluated by means of the Functional Assessment of Cancer Therapy—Lung (FACT-L) Japanese version and the QoL Questionnaire for Cancer Patients Treated with Anticancer Drugs (QoL-ACD), before treatment, immediately before the second cycles of chemotherapy, and 3 and 6 months after the start of treatment [22–24].

statistical analysis and monitoring

The primary end point of this study was overall survival (OS), and the secondary end points were response rate, response duration, time to progressive disease (TTP), time to treatment failure (TTTF), adverse event, and QoL. The 1-year survival rate of the control group in this study was estimated to be 43% based on the data in published papers, and the 1-year survival rate in the other treatment group was expected to be 50%. The lower equivalence limit for 1-year survival rate was set as '−10%'. The criterion for the non-inferiority of each treatment was a lower limit of the two-sided 95% confidence interval (CI) of the 1-year survival rate of treatment minus that of control larger than the lower equivalence limit. Because the non-inferiority of each treatment versus the control was to be evaluated independently, a separate null hypothesis was stated for each treatment, and for that reason no multiple comparison adjustment was included in the study. Based on the above conditions and binomial distribution, 135 patients were needed per arm for a one-sided Type I error of 2.5% and 80.0% power. In view of the possibility of variance inflation due to censoring, the sample size was set at 600 (150 per arm).

Central registration with randomization, monitoring, data collection, and the statistical analyses were independently carried out by a contract research organization (EPS Co., Ltd, Tokyo, Japan).

results

patient characteristics

From October 2000 to June 2002, a total of 602 patients were registered by 44 hospitals in Japan. All patients had been followed up for >2 years, and 447 patients had died as of June 2004. Of the 602 patients registered, 151 were allocated to the reference treatment, IP, and 150, 151, and 150 patients were allocated to TC, GP, and NP, respectively. Since 10 patients did not receive chemotherapy and 11 patients were subsequently found to be ineligible, 592 patients were assessable for toxicity and 581 patients were assessable for efficacy. Four patients did not receive chemotherapy due to electrolytic disorder, fever, symptomatic brain metastases, and rapid tumor progression in IP, two patients due to refusal and pneumonia in TC, four patients due to lower WBC counts (two patients), rapid tumor progression, and nephritic syndrome in NP. Two patents were ineligible due to wrong stage in IP, two patients were wrong stage and one patient had double cancer in TC, two patients were wrong diagnosis, one patient had massive pleural effusion, one patient received prior chemotherapy in GP, one patient had no target lesions in NP. Age, gender, PS, stage, and LDH and albumin values were well balanced in each arm (Table 1). Fewer patients with adenocarcinoma and more patients with squamous cell carcinona were, however, entered in three experimental arms than in IP.

objective tumor response and response duration

Objective tumor response is shown in Table 2. Forty-five partial responses occurred in the 145 assessable patients in the reference arm, IP, for an objective response rate of 31.0% with a median response duration of 4.8 months. The response rate and median response duration were 32.4% and 4.0 months in TC, 30.1% and 3.5 months in GP, and 33.1% and 3.4 months in NP. The response rates in TC, GP, and NP were not statistically different from the rate in IP according to the results of the χ^2 test.

Table 1. Patient characteristics and treatment delivery

	Cisplatin + irinotecan	Carboplatin + paclitaxel	Cisplatin + gemcitabine	Cisplatin + vinorelbine
Assessable patients	145	145	146	145
Gender (male/female)	97/48	99/46	101/45	101/44
Age, median (range)	62 (30–74)	63 (33–74)	61 (34–74)	61 (28–74)
PS (0/1)	44/101	44/101	45/101	45/100
Histology				
Adenocarcinoma	121	104	108	109
Squamous cell carcinoma	16	31	29	29
Others	8	10	9	7
Stage (IIIB/IV)	31/114	28/117	30/116	26/119
No. of cycles				
Mean ± SD	3.0 ± 1.3	3.5 ± 1.5	3.2 ± 1.2	3.1 ± 1.3
Median	3	3	3	3
Range	1–7	1–10	1–7	1–8

PS, performance status; SD, standard deviation.

Table 2. Survival, TTP, TTTF, response rate, and response duration

	N	Median survival months	1-year survival (%)	Difference from IP	2-year survival (%)	TTP (median) months	TTTF (median) months	Response rate (%)	Response duration (median) months
Cisplatin + irinotecan	145	13.9	59.2	–	26.5	4.7	3.3	31.0	4.8 ($n = 45$)
Carboplatin + paclitaxel	145	12.3	51.0	−8.2% (95% CI −19.6% to 3.3%)	25.5	4.5 ($P = 0.355$)[a]	3.2 ($P = 0.282$)[a]	32.4 ($P = 0.801$)[b]	4.0 ($n = 47$)
Cisplatin + gemcitabine	146	14.0	59.6	0.4% (95% CI −10.9% to11.7%)	31.5	4.0 ($P = 0.170$)[a]	3.2 ($P = 0.567$)[a]	30.1 ($P = 0.868$)[b]	3.5 ($n = 44$)
Cisplatin + vinorelbine	145	11.4	48.3	−10.9% (95% CI −22.3% to 0.5%)	21.4	4.1 ($P = 0.133$)[a]	3.0 ($P = 0.091$)[a]	33.1 ($P = 0.706$)[b]	3.4 ($n = 48$)

[a]Compared with IP by the generalized Wilcoxon test.

[b]Compared with IP by the χ^2 test.

CI, confidence interval; IP, cisplatin plus irinotecan; TTP, time to progressive disease; TTTF, time to treatment failure.

OS, TTP disease, and TTTF

OS and TTP are shown in Figure 1. Median survival time (MST), the 1-year, and 2-year survival rate in IP were 13.9 months, 59.2%, and 26.5%, respectively. The MSTs, 1-year, and 2-year survival rates were, respectively, 12.3 months, 51.0%, and 25.5% in TC; 14.0 months, 59.6%, and 31.5% in GP; and 11.4 months, 48.3%, and 21.4% in NP. The lower limits of the 95% CI of the difference in 1-year survival rate between IP and TC (−19.6%), GP (−10.9%), and NP (−22.3%) were below −10%, which was considered the lower equivalence limit (Table 2). Thus, the results did not show non-inferiority in three experimental regimens compared with reference treatment. Median TTP and median TTTF were 4.7 and 3.3 months, respectively in IP. Median TTP and TTTF were, respectively, 4.5 and 3.2 months in TC, 4.0 and 3.2 months in GP, and 4.1 and 3.0 months in NP. There were no statistical differences in either TTP or TTTF in TC, GP, or NP, compared with IP according to the results of the generalized Wilcoxon test (Table 2).

hematologic and non-hematologic toxicity

In IP, 47.6% and 83.7% of patients developed grade 3 or worse leukopenia and neutropenia, respectively (Table 3). The incidences of grade 3 or worse leukopenia (33.1%, $P = 0.010$) and neutropenia (62.9%, $P < 0.001$) were significantly lower in GP than in IP. The incidence of grade 3 or worse leukopenia (67.1%, $P < 0.001$) was significantly higher in NP than in IP. Grade 3 or worse thrombocytopenia developed in 5.4% of the patients in IP, and the incidence was significantly higher in GP (35.1%, $P < 0.001$). The incidence of febril neutropenia in IP was 14.3%, and was significantly lower in GP (2.0%, $P < 0.001$).

Grade 2 or worse nausea, vomiting, anorexia, and fatigue occurred in 60.5%, 51.0%, 65.3%, and 38.8%, respectively, of the patients in IP. The incidences of grade 2 or worse nausea (TC: 25.0%, $P < 0.001$, NP: 47.3%, $P = 0.022$), vomiting (TC: 22.3%, $P < 0.001$, NP: 36.3%, $P = 0.011$), and anorexia (TC: 32.4%, $P < 0.001$, NP: 49.3%, $P = 0.005$) were significantly lower in TC and NP than in IP. Grade 2 or worse diarrhea was

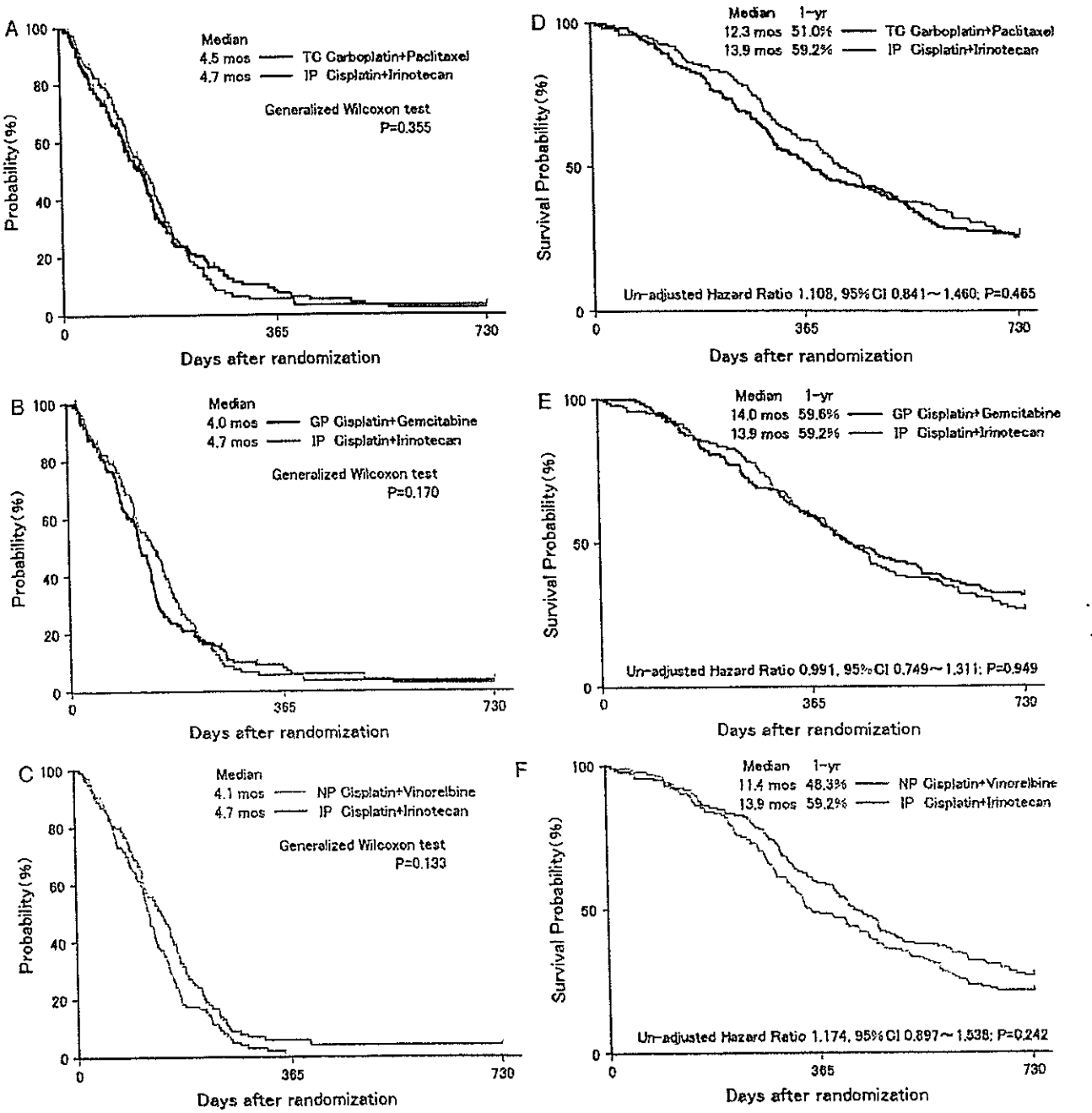

Figure 1. Overall survival (OS) and time to progressive (TTP) disease. TTP and OS in the carboplatin plus paclitaxel (TC) (A, D), cisplatin plus gemcitabine (GP) (B, E), and cisplatin plus vinorelbine (NP) (C, F) were not statistically significantly different from the values in the cisplatin plus irinotecan.

significantly less frequent in TC (6.8%), GP (8.6%), and NP (11.6%) than in IP (48.3%, $P < 0.001$). The incidences of grade 2 or worse sensory neuropathy (16.9%, $P < 0.001$), arthralgia (21.6%, $P < 0.001$), and myalgia (17.6%, $P < 0.001$) were significantly higher in TC than in IP. Grade 2 alopecia occurred in 30.6% of the patients in IP, and its incidence was significantly higher in TC (44.6%, $P = 0.013$) and significantly lower in GP (15.2%, $P = 0.001$) and NP (8.9%, $P < 0.001$). Grade 2 injection site reactions were more frequent in NP (26.7%) than in IP (4.8%, $P < 0.001$).

A total of five patients died of treatment-related toxicity: three in IP (cerebral hemorrhage, interstitial pneumonia, acute circulatory failure/disseminated intravascular coagulation: 2.0%), one in TC (acute renal failure: 0.7%), and one in NP (pulmonary embolism: 0.7%).

second-line treatment

Data on second-line treatment, but not third-line or later treatment, was available in this study, and they showed that

Table 3. Toxicity

	IP (n = 147)			TC (n = 148)			GP (n = 151)			NP (n = 146)		
	Grade (%)			Grade (%)			Grade (%)			Grade (%)		
	1	2	3	1	2	3	1	2	3	1	2	3
Leukocytes	42	43	5	39	42	3	40	31[a]	2[a]	25	51[b]	16[b]
Neutrophils	11	39	45	5	19	69	21	40	23[a]	5	16	72
Hemoglobin	42	24	7	42	13[a]	2[a]	44	22	5	43	25	5
Platelets	6	5	1	9	11	0	22	35[b]	0[b]	3	1[a]	0[a]
Febrile neutropenia	–	14	0	–	18	0	–	2[a]	0[a]	–	18	0
Nausea	32	29	–	14[c]	11[c]	–	35	23	–	33[c]	14[c]	–
Vomiting	38	13	0	17[c]	5[c]	0[c]	34	14	0	29[c]	7[c]	0[c]
Anorexia	30	33	2	15[c]	17[c]	1[c]	31	26	1	29[c]	20c	1[c]
Fatigue	27	12	1	26	2	1	17[c]	3[c]	0[c]	23[c]	3[c]	0[c]
Diarrhea	33	15	1	4[c]	3[c]	0[c]	7[c]	2[c]	0[c]	8[c]	4[c]	0[c]
Constipation	27	7	0	30	8	0	33	9	0	40[d]	14[d]	0[d]
Neuropathy, motor	1	0	0	1	1	1	0	0	0	0	0	0
Neuropathy, sensory	1	0	0	14[d]	3[d]	0[d]	0	0	0	0	0	0
Alopecia	31	–	–	45[d]	–	–	15[c]	–	–	9[c]	–	–
Arthralgia	2	0	0	20[d]	2[d]	0[d]	0	0	0	1	0	0
Myalgia	1	0	0	16[d]	2[d]	0[d]	0	0	0	1	1	0
Injection site reaction	5	0	–	5	0	–	5	0	–	27[d]	0[d]	–
Pneumonitis	0	1	1	0	1	0	0	0	0	0	1	0
Creatinine	8	1	0	2[c]	0[c]	0[c]	7	0	0	8	1	0
AST	7	1	1	5	1	0	6	3	0	1	3	0
Fever	2	0	0	5	1	0	1	0	0	1	0	0
Treatment-related death	3 (2.0%)			1 (0.7%)			0			1 (0.7%)		

[a]Incidence of grade 3 or 4 toxicity significantly ($P < 0.05$) lower than that with IP.

[b]Incidence of grade 3 or 4 toxicity significantly ($P < 0.05$) higher than that with IP.

[c]Incidence of grade 2 or worse toxicity is significantly ($P < 0.05$) lower than that with IP.

[d]Incidence of grade 2 or worse toxicity significantly ($P < 0.05$) higher than that with IP.

GP, cisplatin plus gemcitabine; IP, cisplatin plus irinotecan; NP, cisplatin plus vinorelbine; TC, carboplatin plus paclitaxel.

AST, aspartate aminotransferase; –, no category in the criteria.

60%–74% of the patients received chemotherapy and 6%–9% received thoracic irradiation as second-line treatment (Table 4). The percentages of patients in each treatment group who received second-line chemotherapy were not significantly different ($P = 0.081$).

quality of life

The details of the QoL analysis will be reported elsewhere. No statistically significant difference in global QoL was observed among the four treatment groups based on either the FACT-L Japanese version or the QoL-ACD. Only the physical domain evaluated by QoL-ACD was significantly better in TC, GP, and NP than in IP.

discussion

Many randomized phase III studies have compared platinum-plus-new-agent doublets in NSCLC, but, this is the first to evaluate the efficacy of an irinotecan-containing regimen in comparison with other platinum-plus-new-agent doublets in NSCLC [14–17]. Although non-platinum-containing chemotherapy regimens are used as alternatives, doublets of platinum and a new-generation anticancer agent, such as TC, GP, and NP, are considered standard chemotherapy regimens for advanced NSCLC worldwide [13–17, 25]. Although the non-inferiority of none of the three experimental regimens could be confirmed in this study, no statistically significant differences in response rate, OS, TTP, or TTTF were observed between the reference regimen and the experimental regimens. All four platinum-based doublets have similar efficacy against advanced NSCLC but different toxicity profiles. Nevertheless, IP was still regarded as the reference regimen in this study because the non-inferiority of none of the three experimental regimens could be confirmed.

OS in this study was relatively longer than previously reported. The estimated 1-year survival rate in the reference arm was 43%, but the actual 1-year survival rate was 59.2%, much higher than expected. The MSTs reported for patients treated with TC, GP, and NP in recent phase III studies have ranged from 8 to 10 months, and in the present study they were 12.3, 14.0, and 11.4 months, respectively [14–17]. One reason for the good OS in this study was the difference in patient selection criteria, for example exclusion of PS2 patients. Ethnic differences in pharmacogenomics have also been indicated as a possible reason for the good OS in this study [26]. The OS in IP in this study, however, was better than in previous Japanese studies [18, 19]. TTP in this study ranged from 4.0 to 4.7 months, and was similar to the TTP of 3.1–5.5 months reported in the literature [15, 16]. OS not TTP was longer in this study

Table 4. Second-line treatment

	Cisplatin + irinotecan	Carboplatin + paclitaxel	Cisplatin + gemcitabine	Cisplatin + vinorelbine	
Number of patients	145	145	146	145	
Chemotherapy	107 (74%)	87 (60%)	101 (69%)	95 (66%)	$P = 0.081$
Docetaxel	39	25	50	51	
Gefitinib	11	9	18	12	
Paclitaxel	15	14	7	11	
Gemcitabine	24	28	17	28	
Vinorelbine	9	12	2	9	
Irinotecan	15	4	3	3	
Thoracic irradiation	8	10	13	10	

than previously reported, and higher 2-year survival rates, 21.4%–31.5%, were observed in the minimum 2-year follow-up in this study. Second-line or later treatments may affect survival, because docetaxel has been established as standard second-line chemotherapy for advanced NSCLC [27, 28]. Gefitinib is also effective as second-line or later chemotherapy for advanced NSCLC, especially in Asian patients, never smokers and patients with adenocarcinoma [29–32].

The toxicity profile of each treatment differed and the toxicity of all four regimens was well tolerated. Overall QoL was similar in the four platinum-based doublets. Only physical domain QoL evaluated by the QoL-ACD was statistically better in TC, GP, and NP than in IP. This finding is presumably attributable to the fact that diarrhea is a statistically less frequent adverse effect of TC, GP, and NP than of IP.

In conclusion, all four platinum-based doublets had similar efficacy for advanced NSCLC but different toxicity profiles. All the four regimens can be used to treat advanced NSCLC patients in clinical practice.

appendix

Institutions of the FACS Cooperative Group: National Hospital Organization (NHO) Hokkaido Cancer Center, Tohoku University Hospital, Yamagata Prefectural Central Hospital, Niigata Cancer Center Hospital, Tochigi Cancer Center, NHO Nishigunma National Hospital, Saitama Cancer Center, National Cancer Center Hospital East, Chiba University Hospital, National Cancer Center Hospital, Tokyo Medical University Hospital, Japanese Foundation for Cancer Research, Kanagawa Cancer Center, Yokohama Municipal Citizen's Hospital, Kanagawa Cardiovascular and Respiratory Center, Aichi Cancer Center Hospital, Prefectural Aichi Hospital, Nagoya City University Hospital, NHO Nagoya Medical Center, Nagoya University Hospital, Gifu Municipal Hospital, NHO Kyoto Medical Center, Osaka City General Hospital, Osaka City University Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, NHO Toneyama Hospital, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Kinki University School of Medicine, Rinku General Medical Center Izumisano Municipal Hospital, Kobe Central General Hospital, The Hospital of Hyogo College of Medicine, Hyogo Medical Center for Adults, Tokushima University Hospital, Kagawa Prefectural Central Hospital, NHO Shikoku Cancer Center Hospital, Hiroshima University Medical Hospital, NHO Kyushu Cancer Center Hospital, Kyushu University Hospital, National Nagasaki Medical Center, Nagasaki Municipal Hospital, Nagasaki University Hospital of Medicine and Dentistry, Kumamoto Chuo Hospital, Kumamoto Regional Medical Center, NTT West Osaka Hospital.

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Seminars in Oncology

Geographic Variation in the Second-Line Treatment of Non–Small Cell Lung Cancer

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Although there is broad agreement on management options for treating different stages of non–small cell lung cancer (ie, surgery for stage I and II disease, combined treatment modalities for stage III disease, and platinum-based chemotherapy as initial treatment for appropriate patients with stage IV disease), there is considerable geographic variation in practice patterns. These variations reflect a number of factors, including health care economics, the influence of national and regional regulatory bodies, the nature of physician and patient interaction, and probable biological differences between different populations in terms of drug metabolism and inherent susceptibility to both drug activity and toxicity. The approaches taken by three different geographic regions, the United States, European Union, and Japan, are evaluated. Clinically, the most striking differences in activity and toxicity between different regions have been seen with the epidermal growth factor receptor inhibitors gefitinib and erlotinib. Japanese patients experience significantly greater response and a greater degree of interstitial lung disease than patients in the European Union and North America (ie, US and Canada). Similar differences in efficacy and toxicity have also been noted with cytotoxic chemotherapy agents in the first-line setting. These geographic and ethnic differences in toxicity and efficacy will need to be considered in the design and comparison of future clinical trials.
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Lung cancer is the most lethal malignancy in the developed world, and was expected to account for over one million deaths worldwide in 2005.[1] Non–small cell lung cancer (NSCLC) accounts for approximately 85% of these cases.[2] The vast majority of cases are secondary to tobacco use. Other etiologies include asbestos and radon exposure as well as a genetic contribution.

Although standards of care have been established for different stages of the disease, there is considerable geographic variation in practice patterns. Three major geographic factors influence the choice of second- and third-line therapy. First is the influence of the regulatory agencies that govern the approval of antineoplastic agents. Second is the influence of the specific national healthcare system, including factors governing reimbursement to patients and physicians for treatment. Finally, and most significantly, is the emerging recognition that there are biological differences between different populations in terms of drug metabolism and inherent efficacy. This article will briefly review the approaches taken to second-line therapy in three different areas of the world: the United States, European Union (EU), and Japan.

Overview of Second-Line Therapy

Docetaxel

The first agent to show unequivocal activity in the second-line treatment of NSCLC was docetaxel. A National Cancer Institute of Canada trial compared docetaxel at 75 mg/m^2 or 100 mg/m^2 versus best supportive care. This trial found superior quality and length of life for patients treated with 75 mg/m^2 docetaxel.[3] An industry-sponsored study in the United States compared docetaxel at either 75 or 100 mg/m^2 versus a physician choice of either vinorelbine or ifosfamide. Again, quality of life and survival were superior for docetaxel 75 mg/m^2.[4] The concordant results of these two trials support

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the conclusion that docetaxel 75 mg/m^2 every 3 weeks has a clear role in this setting. Docetaxel has been approved for treatment of previously treated NSCLC in the United States, EU, and Japan.

Pemetrexed

Pemetrexed, a new antifolate agent that has shown activity in mesothelioma, has been tested in the second-line treatment of NSCLC. A phase III trial randomizing patients to either pemetrexed (500 mg/m^2 every 3 weeks with vitamin B_{12} and folate supplementation) or docetaxel (75 mg/m^2 every 3 weeks) showed a similar level of activity but superior tolerability.[5] There was considerably less myelotoxicity and alopecia in the pemetrexed arm, and significantly fewer patients required hospitalization after treatment than with docetaxel. Activity, in terms of response rate, median survival time, and 1-year survival rate, was superimposable for pemetrexed and docetaxel. Pemetrexed has been approved in the United States and EU for the second-line treatment of advanced NSCLC.

Gefitinib

Gefitinib was the first drug to receive approval for third-line therapy of NSCLC anywhere in the world (Japan). This approval was controversial as its basis was response rate rather than a more unequivocal outcome of patient benefit, such as survival rate.[6] The drug had previously failed to show benefit (in terms of response or survival) as a first-line treatment when combined with standard chemotherapy.[7,8]

Two large phase II trials of gefitinib monotherapy, the Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) 1 and IDEAL 2 studies, evaluated the agent in pretreated NSCLC. Both studies determined response and survival. The IDEAL 1 trial, conducted primarily in Japan and Europe, also evaluated the safety profile and symptom improvement, while the IDEAL 2 trial, conducted in North America, evaluated symptom improvement as an additional primary endpoint.[9,10] The response rates for dosages of 250 mg/day and 500 mg/day were 18.4% and 19% in IDEAL 1, and 12% and 9% in IDEAL 2, respectively. Many patients, even those with a poor performance status (ie, performance status 2–3) experienced symptom improvement (most notably in pulmonary symptoms of dyspnea and chest pain) within 2 weeks of starting gefitinib treatment. This improvement in quality-of-life scales, though questionable as there was no randomization against either best supportive care or another agent, was the major impetus for granting conditional approval to market the agent in the United States. Approval was granted under the provision that appropriate randomized trials be conducted. Gefitinib has not received approval in the EU, although it has been approved in Switzerland.

Subset analysis shows that female sex, adenocarcinoma (and, in particular, bronchioloalveolar histology), and nonsmoking status are predictors of response.[10,11] Female sex was a particularly strong predictor in both IDEAL trials. In the primarily North American IDEAL 2 study, 50% of women experienced symptomatic response versus 31% of men ($P = .006$). Radiographic regression was also seen in 19% of women versus only 3% of men ($P = .001$). Two groups in Boston, MA have recently reported that mutations in the aATP-binding pocket of the epidermal growth factor receptor (EGFR) tyrosine kinase (TK) domain predict for clinical benefit from gefitinib.[12,13] While others have confirmed the presence of mutations, the role of mutations versus other alterations in *EGFR* (copy number, expression as measured by fluorescence in situ hybridization) have also been proposed as predictors of response to EGFR TK inhibitors (TKIs). It remains unclear as to whether any of these molecular variables predict independently for outcome.[14]

The role of gefitinib has recently been questioned because of the results of the Iressa Survival Evaluation in Lung Cancer (ISEL) trial.[15] This trial, undertaken in countries in which gefitinib had not received approval (ie, countries other than the United States and Japan) randomized patients between gefitinib and placebo. The ISEL trial was conducted in cooperation with 210 institutes in 28 countries (not including Japan). An advantage was shown in terms of response rate.[15] However, a trend toward improved survival did not achieve statistical significance. The subset analysis in Asian and non-Asian patients showed that female sex and adenocarcinoma histology were more common characteristics in Asian patients (Table 1). The US Food and Drug Administration has recently restricted use of gefitinib to patients who are currently being treated with the agent and who demonstrate benefit, and those enrolled in clinical trials.

Erlotinib

Erlotinib is an agent very similar to gefitinib in terms of structure and activity. It too has been evaluated as a second-line drug in the treatment of NSCLC, showing 'promising results' in terms of response and survival in phase II trials.[16]

However, unlike gefitinib, a phase III trial was unequivocally positive. The National Cancer Institute of Canada led a study (JBR-21) comparing erlotinib with best supportive care in third-line therapy. This large study (more than 700 patients) provided definitive evidence of benefit in terms of survival for this agent.[17] Improvements in response (9% v >1%), median survival (6.7 v 4.7 months; $P < .001$), 1-year survival (31% v 21%), and symptomatology (cough, dyspnea, pain) were observed.[17] Erlotinib has been approved in the United States and EU for the second- and third-line therapy of advanced NSCLC.

Geographic Variations in Treatment

Variations in the efficacy and safety of second-line NSCLC therapies have been observed across geographic regions, and have had an impact on the choice of treatment options within the three key pharmaceutical markets of the United States, the EU, and Japan.

United States

As described above, three agents have been approved by the US Food and Drug Administration for use in the second-line

Table 1 A Comparison of Gefitinib Monotherapy Data Across Geographic Regions

Characteristics	Japanese[40]	Non-Japanese[40]	American[10]	Asian[15]	Non-Asian[15]
No. of patients by gefitinib dose					
250 mg/m²	51	53	102	235	894
500 mg/m²	51	55	114	0	0
Demographics					
Median age (yrs)	60	61	61	61	62
Age range (yrs)	28–77	38–85	30–84	NA	NA
Female (%)	37	22	43	40	31
PS 0–1 (%)	91	83	80	72	64
Stage IV (%)	80	81	89	NA	NA
Adenocarcinoma (%)	76	56	66	64	44
No. of prior chemotherapy regimens (%)					
1	53	59	1	54	48
2	47	41	41	46	52
3 or more	0	0	58	0	0
Treatment efficacy					
Response rate (%)	28	10	10	12	7
Median survival (mos)	12	9.9	6–7	9.5	5.2
1-year survival (%)	50	NA	24–27	44	21
Grade 3–4 toxicity (%)					
Diarrhea	4	3	3	NA	NA
Skin rash	3	5	2	NA	NA
ALT elevation	7	1	1	NA	NA
Interstitial lung disease	2	0	0	2	0.001

Abbreviations: ALT, alanine aminotransferase; NA, not applicable; PS, performance status.

setting: docetaxel, pemetrexed, and erlotinib. Erlotinib also has approval in the third-line setting. Gefitinib, which had been granted an accelerated approval based on the phase II data from the IDEAL studies,[18] has been re-labeled in light of data from the ISEL trial.[19] At present it may only be prescribed in a non-investigational setting for patients who are already receiving the agent and who have demonstrated benefit.

Agent Selection. Controversy exists over which of the three approved agents should be used in the second-line setting. Several factors enter into consideration in the United States. First, docetaxel has also received approval as a first-line agent and is frequently used in this setting with carboplatin or cisplatin. Therefore, a patient who has already received this agent and has progressed would not be a suitable candidate to receive the drug again in the second-line setting. Second, there are no trials comparing the value (in terms of patient benefit) of any of the second-line agents in this setting. As a result, clinical judgement and economic issues are relevant. Third, there appears to be an emerging trend for physicians to use erlotinib in patients who have demonstrated the greatest degree of benefit, ie, non-smokers, women, those patients with adenocarcinoma histology, and those with Asian ancestry. It is possible that selection of patients in the future will also be driven by objective biological markers, ie, the presence of *EGFR* gene mutations or increased *EGFR* copy number. Pemetrexed is therefore used in the remaining population. For most practitioners the superimposable results in terms of survival for pemetrexed and docetaxel, coupled with its superior toxicity profile, make pemetrexed the preferred agent when both drugs are considered for second-line therapy.

Economics. Economic issues are of considerable importance given the expense of the agents. Most insurance programs in the United States will cover the cost of administration of intravenous agents but vary considerably regarding the coverage for oral agents. The cost of gefitinib (USD $2,000 to $3,000/month) is considerable. An assistance program sponsored by the manufacturer is available.

European Union

It is difficult to separate any side effects or outcome differences between the EU countries and North America. Several of the trials described above, including JBR-21 and the randomized trial of pemetrexed versus docetaxel, were conducted with significant accrual from European countries. Approvals within Europe are granted by the European Medicines Agency; a separate Committee for Proprietary Medicinal Products provides clinical expertise for the review process. Pemetrexed, erlotinib, and docetaxel are the agents currently approved in the EU for use as second-line therapy.

Japan

Japan was the first country to approve gefitinib for use in the treatment of lung cancer. Drug approvals in Japan are granted by the Ministry of Health, Labor, and Welfare. The Japanese have a significant preference for oral medications, a factor that is likely to have contributed to the rapid approval of gefitinib.[20]

Approximately 50% of the patients enrolled into the IDEAL 1 trial were Japanese.[9] The remainder were from Europe, Australia, and South Africa, and were predominantly white. Significant differences emerged regarding both efficacy and toxicity; there was no comparison of survival. The response rate was clearly higher for the Japanese (27.5% v 10.4%; $P = .0023$). There were no pharmacokinetic differences to explain this response difference. However, in a multivariate analysis, ethnicity did not emerge as an independent factor for response. Baseline factors such as performance status, sex, and histology appear to explain the ethnic differences.

In the ISEL study, the response rate and median survival time were 12% and 9.5 months in Asian patients and 7% and 5.2 months in non-Asian patients, respectively (Table 1).[15] Mutations of the *EGFR* gene, recently identified in patients with gefitinib-responsive lung cancer,[12,13] correlated well with clinical response to gefitinib and patient survival in retrospective case series studies.[21,22] The relatively high frequency of the mutations in East Asian patients (27% to 34%), compared with 14% or less in American patients, may explain the geographical difference in the efficacy of gefitinib.[12,23] The frequencies of grade 3–4 common toxicities of gefitinib, including diarrhea, skin rash, and alanine transferase elevation, were the same among the study populations (Table 1).

Treatment-Associated Interstitial Lung Disease. Because of the limited number of patients evaluated in clinical trials, it is sometimes difficult to identify and analyze uncommon toxicity before marketing a drug. Interstitial lung disease (ILD) associated with administration of gefitinib came to light in October 2002, 4 months after approval of this agent in Japan.[24] In the IDEAL studies, two Japanese patients developed grade 3–4 ILD (2%), while no patients outside Japan experienced ILD. In the ISEL study, the incidence of grade 3–4 ILD was 2% in Asian patients and .001% in non-Asian patients. In a retrospective evaluation of 112 Japanese patients, the incidence of ILD was 5.4%. The primary risk factor was a prior history of pulmonary fibrosis.[24] Between July 2002 and December 2004, there were 86,800 patients with NSCLC who were estimated to have received gefitinib in Japan. According to the Ministry of Health, Labor, and Welfare 1,473 patients were suspected of having ILD associated with the use of gefitinib and 588 patients died of ILD.[25] A prospective survey of gefitinib toxicity in 3,354 NSCLC patients treated at 698 hospitals in Japan between June and December 2003 showed that the incidence of ILD was 5.8% and the mortality rate was 2.5%.[26] Risk factors for the development of ILD identified in the Japanese population were preceding pulmonary fibrosis, smoking history, poor performance status, and male sex.[24,26,27] ILD tends to appear rapidly after initiation of therapy.[28]

In an analysis by the US Food and Drug Administration comparing the incidence of ILD associated with gefitinib treatment in North America and Japan, there was an incidence of approximately 2% from a Japanese postmarketing experience and 0.3% in approximately 23,000 patients in the United States expanded-access program.[18]

It is interesting to note that ILD has been associated with weekly docetaxel therapy in Japanese patients. In a phase II study, docetaxel as a single agent was administered at a dose of 35 mg/m^2 on days 1, 8, and 15 every 4 weeks in 48 patients with advanced or recurrent NSCLC. Of these, 33 patients had had no prior chemotherapy and 15 had received one prior chemotherapy treatment. Patients who had previously undergone thoracic radiotherapy, who had preceding ILD or pulmonary fibrosis, or who had severe pulmonary emphysema were excluded from the study. Of the 48 patients in the study, five (10.4%) developed grade 3–4 ILD.[29] The incidence of ILD associated with weekly administration of docetaxel in other countries varies with reports: grade 3–4 pulmonary toxicity was noted in seven of 35 (20%) patients in a Spanish study,[30] one of 63 (1.6%) in a French study,[31] none of 110 patients in an Italian study, and none of 30 patients in an American study.[32,33] It is unclear from these data whether the development of ILD represents a toxicity to which Japanese patients are predisposed, or is a diagnosis that is made more frequently in Japan for other reasons.

Differences in Efficacy and Toxicity. The differences between Western populations and the Japanese (and other non-Western ethnicities) in both the efficacy and toxicity of an anticancer agent are an emerging issue. Two recent trials comparing carboplatin plus paclitaxel with other combinations for first-line therapy of NSCLC were conducted in the United States (by the Southwest Oncology Group) and Japan (Japan Cooperative Oncology Group, Four Arm Comparative Study).[34] The carboplatin plus paclitaxel arm was similar in both studies (differing only by a slightly lower dose of paclitaxel in the Japanese study), and criteria for entry, dose modifications, toxicity, and response assessment were identical. Considerable differences in toxicity and activity were noted between the two studies. The rate of febrile neutropenia was five-fold greater (16% v 3%; $P < .0001$) in the Japanese trial, while the rate of neuropathy was substantially lower (5% v 16%; $P = .001$). The response rates were similar, while the 1-year survival rate was better in the Japanese trial (51% v 37%; $P = .009$).

Distribution of Genetic Polymorphisms for Thymidylate Synthase

Another area of growing interest in this field is the observation that the activity of antifolate agents may be related to germline differences in the expression of the target enzyme, thymidylate synthase (TS). Pemetrexed, though a multitargeted antifolate, appears to have its primary activity at TS. TS expression is controlled in part by the *TS* enhancer region (*TSER*) within the 5′ untranslated region of the *TS* gene. Recent work has shown that the *TSER* is polymorphic with significant ethnic variation and relates to the activity of the agents. Tandem repeats of 28 base pairs have been identified,

Table 2 Geographic Differences in the Incidence of TSER*3 Polymorphism[35]

Population	Individuals Homozygous for *TSER*3* (%)
White	28
African-American	24
Southwest Asian	40
Chinese	67

and expression of the gene is increased with additional repeats. A triple tandem repeat (*TSER*3*) demonstrates 2.6-fold greater expression than the double repeat (*TSER*2*). There is considerable variation in this polymorphism both within and between ethnic groups (Table 2).[35]

Increased expression of this enzyme can alter both the activity and pharmacology of folate antagonist agents. For example, the activity of 5-fluorouracil activity in colon cancer is influenced by the *TSER* polymorphism.[36] Patients homozygous for *TSER*3* show increased intratumoral levels of TS protein. Higher levels of TS are associated with poorer response rates and survival. In lung cancer, there is evidence from Japanese studies that elevated TS levels correlate with increased proliferation and decreased sensitivity to antifolate agents (specifically 5-fluorouracil).[37,38] Preliminary data indicate that *TS* gene polymorphisms are prognostic for patients treated with platinum-based chemotherapy.[39] Studies are currently in preparation to determine whether *TS* gene polymorphisms are a predictive or prognostic factor (or both) for treatment with pemetrexed in NSCLC.

Conclusion

Second- and third-line treatments have now emerged as a standard of care throughout the world. Regulatory agencies in the United States and EU have approved docetaxel, pemetrexed, and erlotinib for second-line use. Japan was the first country to approve an EGFR TKI (gefitinib) for second-line use. There appears to be a substantially greater response to both gefitinib and erlotinib in Japan, but also a significant risk of life-threatening pneumonitis. Moreover, this variation in efficacy and side-effect profile appears to be present in other Asian populations. These ethnic differences may be surrogates for differences in genetic aspects of drug metabolism or potential differences in tumor susceptibility. The findings of a recent 'common arm' study performed in the United States and Japan in first-line therapy, as well as the studies of the two EGF TKIs, clearly demonstrate that the benefits and risks of anticancer agents may differ between populations. It is clear that the benefits and risks of anticancer agents differ between populations.

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Phase 1 Clinical Study of Pegylated Liposomal Doxorubicin (JNS002) in Japanese Patients with Solid Tumors

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Background: Pegylated liposomal doxorubicin (PLD, JNS002) is a formulation of doxorubicin encapsulated polyethylene-glycol coated liposomes with prolonged circulation time and unique toxicity profile. This phase 1 study was aimed at investigating the maximum tolerated dose (MTD), recommended dose, toxicity, pharmacokinetics, and antitumor activity in Japanese patients with solid tumors.

Methods: Patients with solid tumors not amenable to standard forms of treatment were eligible. PLD was administered as an intravenous infusion every 4 weeks. Dose escalation of PLD was planned from 30 to 60 mg/m^2 in 10 mg/m^2 increments. The pharmacokinetics of total doxorubicin (encapsulated plus non-encapsulated) in plasma were examined for the first cycle of treatment.

Results: Fifteen patients, aged 49–69 (median; 56) years with advanced solid tumors were enrolled. The major non-hematological toxicities were hand–foot syndrome (HFS), rash and stomatitis. Myelosuppression, especially leukopenia and neutropenia were major hematological toxicities. Although HFS was not severe, a delay of doses for subsequent cycles was required with multiple dosing. The peak plasma concentration and the area under the concentration time curve of PLD increased proportionally to the dose. Objective response was observed in one patient and the normalization of tumor marker values in another. These two patients had been diagnosed with ovarian cancer.

Conclusion: The recommended dose for phase 2 clinical studies of PLD in Japanese patients was 50 mg/m^2 every 4 weeks. The encouraging results prompted us to plan a subsequent clinical study of PLD against ovarian cancer.

Key words: Phase 1 study – drug delivery system – Pegylated liposomal doxorubicin – JNS002

INTRODUCTION

Pegylated liposomal Doxorubicin (PLD) is a formulation of doxorubicin hydrochloride encapsulated in long circulating STEALTH® liposomes and formulated for intravenous administration. PLD was designed to enhance the efficacy and reduce the toxicities of doxorubicin such as myelosuppression, alopecia and cardiotoxicity by altering the plasma pharmacokinetics and tissue distribution of the drug.

This pegylated-liposome system can evade non-specific capture by the reticuloendothelial system because the outer shell of the liposome is covered with a hydrophilic PEG. This character is the basis of the so-called 'stealth effect' (1). The diameter of the liposome is small (100 nm) but is still large enough to avoid renal secretion. Meanwhile, in the solid tumor tissues, it was found that solid tumors generally possess the pathophysiological characteristics: hypervasculature, secretion of vascular permeability factors stimulating extravasation of macromolecules within the cancer and absence of effective lymphatic drainage from tumors that impedes the efficient clearance of macromolecules accumulated in solid tumor tissues. These characteristics of solid tumors are the basis of the enhanced permeability and retention effect, the EPR effect (2,3). Taking these data together, conventional low-molecular-weight anticancer agents disappear before reaching the tumor tissues and exerting their cell-killing effect. However, macromolecules and nanoparticles including liposomal carrier should have time to reach, exit from tumor capillaries and stay for a long time in tumor tissue, by means of the EPR effect (2–5). Following intravenous injection of PLD into tumor-bearing mice,

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doxorubicin levels measured in tumors are substantially higher than those seen in animals receiving comparable doses of non-encapsulated drug (6). It appears that PLD accumulates preferentially in tumor tissues with increased microvascular permeability, such as in the case of most tumors with active neoangiogenesis (7,8). At these tumor sites, the accumulating liposomes gradually break down releasing doxorubicin to the surrounding tumor cells (9,10). Antitumor efficacy of PLD has been evaluated in a variety of murine tumor models and human xenograft tumor models. In addition, it was also known to be effective against spontaneously arising malignancies in dogs (11).

Based on the previous clinical data, PLD is an active agent available for the treatment of AIDS-related Kaposi's sarcoma (12,13) and has shown significant activity against some solid tumors, including ovarian and breast cancer, in phase 1 and 2 studies (14–16). Phase 1 study in the USA and Israel of PLD in patients with solid tumor pointed at a major change in the toxicity profile of doxorubicin, characterized by dominant and dose-limiting mucocutaneous toxicities in the form of palmar–plantar erythrodysesthesia (PPE, known also as hand–foot syndrome, HFS) (17) and stomatitis, mild myelosuppression, minimal alopecia and no apparent cardiac toxicity (14). With the aim of establishing an effective treatment against malignant solid tumors using this promising new formulation of doxorubicin hydrochloride, we initiated a clinical study of PLD in Japan. The objectives of this phase 1 study were (i) to determine the maximum tolerated dose (MTD) and recommended dose of PLD, (ii) to identify the toxicity profile, (iii) to assess its pharmacokinetic (PK) profile, and (iv) to observe any antitumor activities.

PATIENTS AND METHODS

Patients

Patients with malignant solid tumors were eligible if they met the following criteria: (i) histologic or cytologic confirmation of malignant solid tumor; (ii) tumors resistant to standard therapies or for which there was no effective treatment; (iii) $\geq$20 years and $\leq$74 years of age; (iv) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; (v) life expectancy of at least 3 months; (vi) no chemotherapy, hormonal therapy, radiation therapy, or surgery within 4 weeks prior to the registration (in case of nitrosoureas or mitomycin for previous treatment: 6 weeks); (vii) adequate bone marrow activity (white blood cell count $\geq$4000/μl and $\leq$12 000/μl, absolute neutrophil count $\geq$2000/μl, platelet count $\geq$100 000/μl, and hemoglobin level $\geq$9.0 g/dl), adequate hepatic function (serum total bilirubin [Tbil] level $\leq$1.5 times the normal upper limit, transaminase $\leq$2.5 times the normal upper limit), adequate renal function (serum creatinine [Cr] level $\leq$1.5 times the normal upper limit), and adequate cardiac function (left ventricular ejection fraction [LVEF] $\geq$55%) by echocardiography; (viii) no severe complications such as uncontrollable infections, heart disease, diabetes and psychogenic disorders; (ix) written informed consent given. Patients with any one of the following conditions were excluded from the study: pregnancy or lactation; symptomatic brain metastasis; doxorubicin dose given prior to study $\geq$300 mg/m^2; a history of hypersensitivity reactions to doxorubicin or ingredients of PLD; hepatic B or C virus or human immunodeficiency virus infection; prior extensive radiation therapy (>30% of bone marrow reserves), and others.

The protocol was approved by the institutional review board of the National Cancer Center and the study was performed in keeping the good clinical practice (GCP) regulations. The study was closed for accrual in March 2004.

Drug Administration

PLD was supplied by Janssen Pharmaceutical K. K. (Tokyo, Japan) as a dispersion including 50 mg of doxorubicin hydrochloride in STEALTH® liposome per vial (2 mg/ml). An amount prescribed less than 90 mg was diluted in 250 ml of 5% glucose solution and that of 90 mg or more was diluted in 500 ml of 5% glucose solution prior to administration. Diluted PLD was infused intravenously at a rate of 1.0 mg/min from the start to the end of infusion to minimize the risk of infusion reactions.

Patients were administered PLD on day 1 of each 28-day cycle and they received two or more cycles in principle. All patients were admitted for the first cycle of treatment to be monitored carefully, giving consideration to unexpected adverse events. Subsequent cycles were performed in the outpatient setting. Although no standard premedication was given, infusion reaction, nausea and vomiting were treated as needed.

STUDY DESIGN

Based on the results of previously reported clinical study (14), the starting dose of PLD was 30 mg/m^2 (Level 1) and dose escalation in 10 mg/m^2 increments was planned up to 60 mg/m^2 (Level 4). At each dose level, three patients were scheduled for entry. Three additional patients were scheduled for treatment at the same dose level if any of the predefined dose limiting toxicities (DLTs) was observed in one of the initial three patients. The MTD was defined as the dose level at which any of the DLTs was observed in two or more of three to six patients. Intrapatient dose escalation was not allowed. The treatment was repeated every 4 weeks, unless patients developed progressive disease or DLTs. In this study the DLTs were defined as follows: (i) grade 3 or more non-hematological toxicity except for nausea/vomiting, anorexia and general malaise; (ii) grade 3 or more febrile neutropenia; (iii) grade 4 hematological toxicity except grade 4 neutropenia not lasting for 5 days, according to the Japanese version of NCI-Common Toxicity Criteria prepared by the Japan Clinical Oncology Group (JCOG). As multiple dosing is required for PLD to show the optimal antitumor effect, the