

# 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<sup>2</sup> on day 1 plus irinotecan 60 mg/m<sup>2</sup> 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<sup>2</sup> on day 1 every 3 weeks (TC); cisplatin 80 mg/m<sup>2</sup> on day 1 plus gemcitabine 1000 mg/m<sup>2</sup> on days 1, 8 every 3 weeks (GP); and cisplatin 80 mg/m<sup>2</sup> on day 1 plus vinorelbine 25 mg/m<sup>2</sup> 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

## 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 ( $\text{paO}_2$ )  $\geq 60$  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  $\text{mg/m}^2$  of cisplatin on day 1 and 60  $\text{mg/m}^2$  of irinotecan on days 1, 8, and 15, and the cycle was repeated every 4 weeks. The second group received 200  $\text{mg/m}^2$  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  $\text{min} \times \text{mg/mL}$  on day 1 and the cycle was repeated every 3 weeks. The third group received 80  $\text{mg/m}^2$  of cisplatin on day 1 and 1000  $\text{mg/m}^2$  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  $\text{mg/m}^2$  of cisplatin on day 1 and 25  $\text{mg/m}^2$  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 patients 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 carcinoma 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  $\chi^2$  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 in 1-year survival 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 ( <i>n</i> = 45)
Carboplatin + paclitaxel	145	12.3	51.0	–8.2% (95% CI –19.6% to 3.3%)	25.5	4.5 ( <i>P</i> = 0.355) <sup>a</sup>	3.2 ( <i>P</i> = 0.282) <sup>a</sup>	32.4 ( <i>P</i> = 0.801) <sup>b</sup>	4.0 ( <i>n</i> = 47)
Cisplatin + gemcitabine	146	14.0	59.6	0.4% (95% CI –10.9% to 11.7%)	31.5	4.0 ( <i>P</i> = 0.170) <sup>a</sup>	3.2 ( <i>P</i> = 0.567) <sup>a</sup>	30.1 ( <i>P</i> = 0.868) <sup>b</sup>	3.5 ( <i>n</i> = 44)
Cisplatin + vinorelbine	145	11.4	48.3	–10.9% (95% CI –22.3% to 0.5%)	21.4	4.1 ( <i>P</i> = 0.133) <sup>a</sup>	3.0 ( <i>P</i> = 0.091) <sup>a</sup>	33.1 ( <i>P</i> = 0.706) <sup>b</sup>	3.4 ( <i>n</i> = 48)

<sup>a</sup>Compared with IP by the generalized Wilcoxon test.

<sup>b</sup>Compared with IP by the  $\chi^2$  test.

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

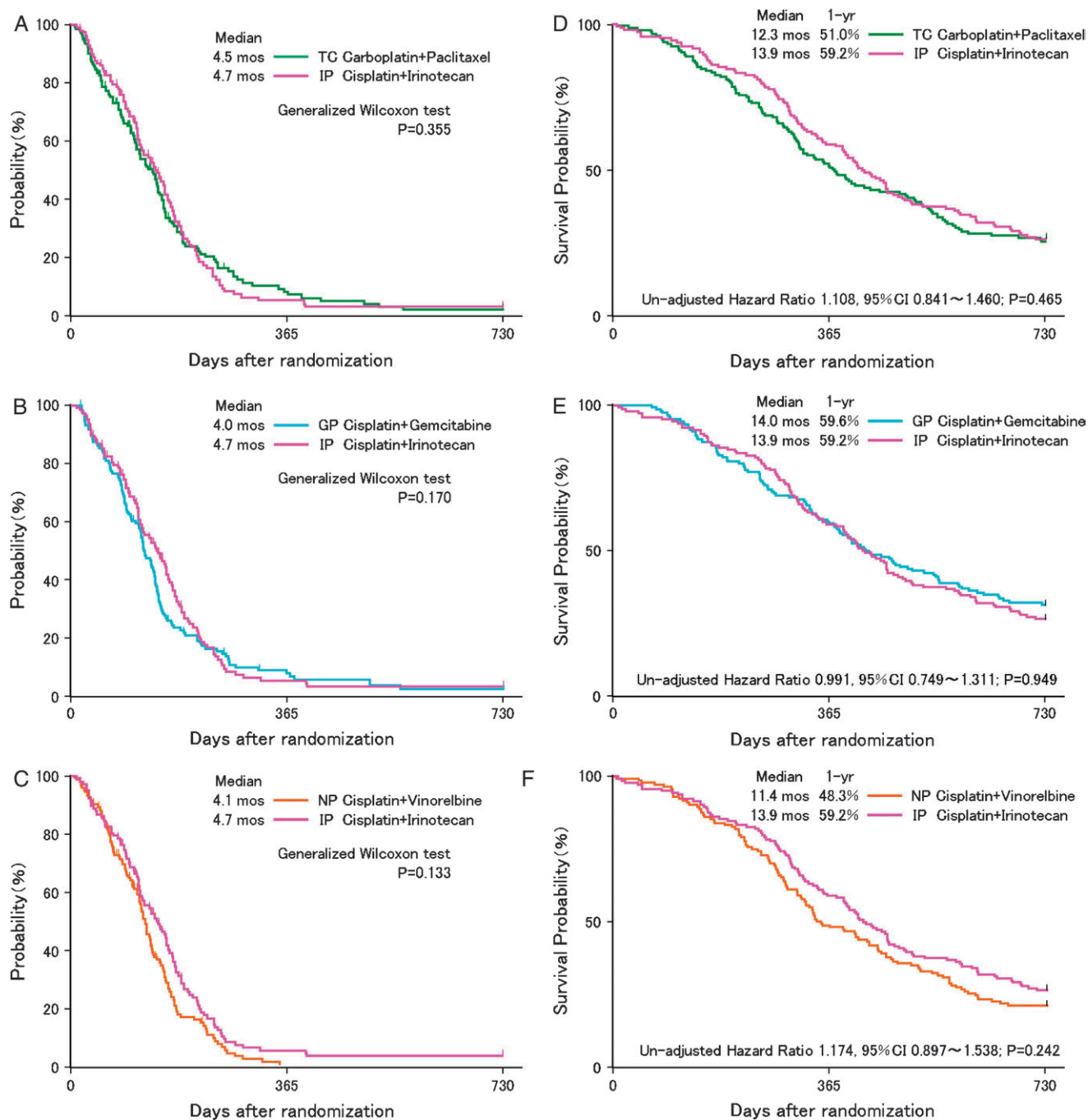
## OS, TTP disease, and TTTF

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 (%)		
	2	3	4	2	3	4	2	3	4	2	3	4
Leukocytes	42	43	5	39	42	3	40	31 <sup>a</sup>	2 <sup>a</sup>	25	51 <sup>b</sup>	16 <sup>b</sup>
Neutrophils	11	39	45	5	19	69	21	40	23 <sup>a</sup>	5	16	72
Hemoglobin	42	24	7	42	13 <sup>a</sup>	2 <sup>a</sup>	44	22	5	43	25	5
Platelets	6	5	1	9	11	0	22	35 <sup>b</sup>	0 <sup>b</sup>	3	1 <sup>a</sup>	0 <sup>a</sup>
Febrile neutropenia	–	14	0	–	18	0	–	2 <sup>a</sup>	0 <sup>a</sup>	–	18	0
Nausea	32	29	–	14 <sup>c</sup>	11 <sup>c</sup>	–	35	23	–	33 <sup>c</sup>	14 <sup>c</sup>	–
Vomiting	38	13	0	17 <sup>c</sup>	5 <sup>c</sup>	0 <sup>c</sup>	34	14	0	29 <sup>c</sup>	7 <sup>c</sup>	0 <sup>c</sup>
Anorexia	30	33	2	15 <sup>c</sup>	17 <sup>c</sup>	1 <sup>c</sup>	31	26	1	29 <sup>c</sup>	20 <sup>c</sup>	1 <sup>c</sup>
Fatigue	27	12	1	26	2	1	17 <sup>c</sup>	3 <sup>c</sup>	0 <sup>c</sup>	23 <sup>c</sup>	3 <sup>c</sup>	0 <sup>c</sup>
Diarrhea	33	15	1	4 <sup>c</sup>	3 <sup>c</sup>	0 <sup>c</sup>	7 <sup>c</sup>	2 <sup>c</sup>	0 <sup>c</sup>	8 <sup>c</sup>	4 <sup>c</sup>	0 <sup>c</sup>
Constipation	27	7	0	30	8	0	33	9	0	40 <sup>d</sup>	14 <sup>d</sup>	0 <sup>d</sup>
Neuropathy, motor	1	0	0	1	1	1	0	0	0	0	0	0
Neuropathy, sensory	1	0	0	14 <sup>d</sup>	3 <sup>d</sup>	0 <sup>d</sup>	0	0	0	0	0	0
Alopecia	31	–	–	45 <sup>d</sup>	–	–	15 <sup>c</sup>	–	–	9 <sup>c</sup>	–	–
Arthralgia	2	0	0	20 <sup>d</sup>	2 <sup>d</sup>	0 <sup>d</sup>	0	0	0	1	0	0
Myalgia	1	0	0	16 <sup>d</sup>	2 <sup>d</sup>	0 <sup>d</sup>	0	0	0	1	1	0
Injection site reaction	5	0	–	5	0	–	5	0	–	27 <sup>d</sup>	0 <sup>d</sup>	–
Pneumonitis	0	1	1	0	1	0	0	0	0	0	1	0
Creatinine	8	1	0	2 <sup>c</sup>	0 <sup>c</sup>	0 <sup>c</sup>	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%)		

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

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

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

<sup>d</sup>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%)	<i>P</i> = 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

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## references

1. Cancer Statistics in Japan 2005: The Editorial Board of the Cancer Statistics in Japan. Tokyo, Japan: Foundation for Promotion of Cancer Research 2005.
2. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995; 311: 899–909.
3. Fukuoka M, Niitani H, Suzuki A et al. A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. *J Clin Oncol* 1992; 10: 16–20.
4. Rowinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med* 1995; 332: 1004–1014.
5. Gelmon K. The taxoids: paclitaxel and docetaxel. *Lancet* 1994; 344: 1267–1272.
6. Hertel LW, Border GB, Kroin JS et al. Evaluation of the antitumor activity of gemcitabine (2',2'-difluoro-2'-deoxycytidine). *Cancer Res* 1990; 50: 4417–4422.
7. Binet S, Fellous A, Lataste H et al. Biochemical effects of navelbine on tubulin and associated proteins. *Semin Oncol* 1989; 16 (2 Suppl 4): 9–14.
8. Kubota K, Watanabe K, Kunitoh H et al. Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. *J Clin Oncol* 2004; 22: 254–261.
9. Le Chevalier T, Brisgand D, Douillard JY et al. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small cell lung cancer: results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994; 12: 360–367.
10. Belani CP, Lee JS, Socinski MA et al. Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer. *Ann Oncol* 2005; 16: 1069–1075.
11. Yana T, Takada M, Origasa H et al. New chemotherapy agent plus platinum for advanced non-small cell lung cancer: a meta-analysis. *Proc Am Soc Clin Oncol* 2002; 21: 328a.
12. Baggstrom MQ, Socinski MA, Hensing TA et al. Third generation chemotherapy regimens (3GR) improve survival over second generation regimens (2GR) in stage IIIB/IV non-small cell lung cancer (NSCLC): a meta-analysis of the published literature. *Proc Am Soc Clin Oncol* 2002; 21: 306a.

13. Hotta K, Matsuo K, Ueoka H et al. Addition of platinum compounds to a new agent in patients with advanced non-small-cell lung cancer: a literature based meta-analysis of randomised trials. *Ann Oncol* 2004; 15: 1782–1789.
14. Kelly K, Crowley J, Bunn PA et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group Trial. *J Clin Oncol* 2001; 19: 3210–3218.
15. Schiller JH, Harrington D, Belani CP et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002; 346: 92–98.
16. Scagliotti GV, De Marinis F, Rinaldi M et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol* 2002; 20: 4285–4291.
17. Fossella F, Pereira JR, von Pawel J et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 Study Group. *J Clin Oncol* 2003; 21: 3016–3024.
18. Negoro S, Masuda N, Takada Y et al. Randomised phase III trial of irinotecan combined with cisplatin for advanced non-small-cell lung cancer. *Br J Cancer* 2003; 88: 335–341.
19. Niho S, Nagao K, Nishiwaki Y et al. Randomized multicenter phase III trial of irinotecan (CPT-11) and cisplatin (CDDP) versus CDDP and vindesine (VDS) in patients with advanced non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1999; 18: 492a.
20. Fukuoka M, Nagao K, Ohashi Y et al. Impact of irinotecan (CPT-11) and cisplatin (CDDP) on survival in previously untreated metastatic non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2000; 19: 495a.
21. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; 92: 205–216.
22. Cella DF, Bonomi AE, Lloyd SR et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer* 1995; 12: 199–220.
23. Kurihara M, Shimizu H, Tsuboi K et al. Development of quality of life questionnaire in Japan: quality of life assessment of cancer patients receiving chemotherapy. *Psychooncology* 1999; 8: 355–363.
24. Matsumoto T, Ohashi Y, Morita S et al. The quality of life questionnaire for cancer patients treated with anticancer drugs (QOL-ACD): validity and reliability in Japanese patients with advanced non-small-cell lung cancer. *Qual Life Res* 2002; 11: 483–493.
25. Pfister DG, Johnson DH, Azzoli CG et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004; 22: 330–353.
26. Gandara DR, Ohe Y, Kubota K et al. Japan-SWOG common arm analysis of paclitaxel/carboplatin in advanced stage non-small cell lung cancer (NSCLC): a model for prospective comparison of cooperative group trials. *Proc Am Soc Clin Oncol* 2004; 22: 618a.
27. Shepherd FA, Dancey J, Ramlau R et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000; 18: 2095–2103.
28. Fossella FV, DeVore R, Kerr RN et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000; 18: 2354–2362.
29. Kris MG, Natale RB, Herbst RS et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA* 2003; 290: 2149–2158.
30. Fukuoka M, Yano S, Giaccone G et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial). *Clin Oncol* 2003; 21: 2237–2246.
31. Takano T, Ohe Y, Kusumoto M et al. Risk factors for interstitial lung disease and predictive factors for tumor response in patients with advanced non-small cell lung cancer treated with gefitinib. *Lung Cancer* 2004; 45: 93–104.
32. Takano T, Ohe Y, Sakamoto H et al. Epidermal growth factor receptor gene mutations and increased copy numbers predict gefitinib sensitivity in patients with recurrent non-small-cell lung cancer. *J Clin Oncol* 2005; 23: 6829–6837.