

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/m² on day 1 plus irinotecan 60 mg/m² 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/m² on day 1 every 3 weeks (TC); cisplatin 80 mg/m² on day 1 plus gemcitabine 1000 mg/m² on days 1, 8 every 3 weeks (GP); and cisplatin 80 mg/m² on day 1 plus vinorelbine 25 mg/m² 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 (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 $\text{min} \times \text{mg/mL}$ 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 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 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 \pm SD	3.0 \pm 1.3	3.5 \pm 1.5	3.2 \pm 1.2	3.1 \pm 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, TTF, 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	TTF (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% to 11.7%)	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)

^aCompared with IP by the generalized Wilcoxon test.

^bCompared with IP by the χ^2 test.

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

OS, TTP disease, and TTF

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 TTF were 4.7 and 3.3 months, respectively in IP. Median TTP and TTF 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 TTF 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

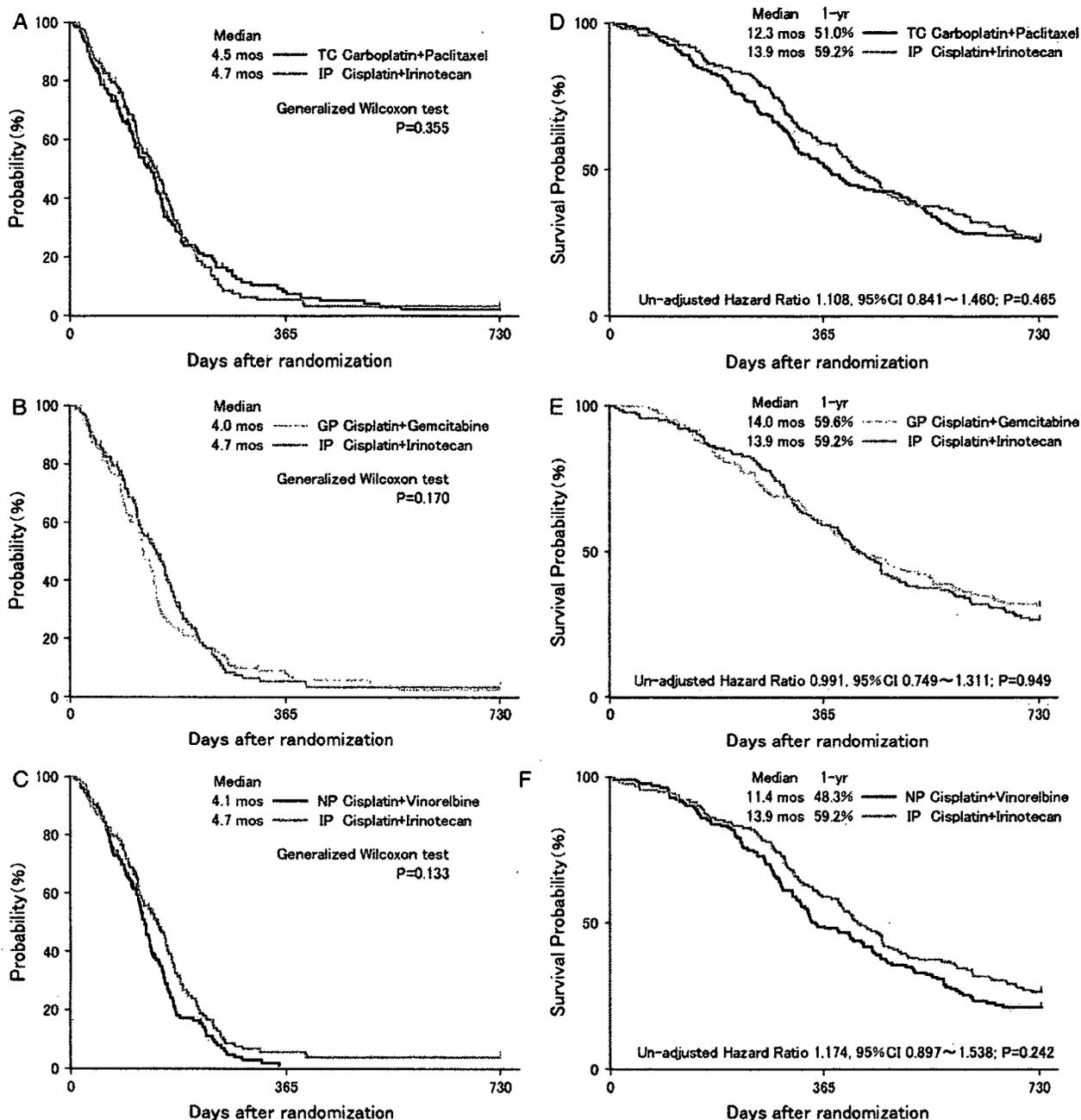


Figure 1. Overall survival (OS) and time to progressive (TTP) disease. TTP and OS in the carboplatin plus paclitaxel (TC) (A, D), cisplatin plus gemcitabine (GP) (B, E), and cisplatin plus vinorelbine (NP) (C, F) were not statistically significantly different from the values in the cisplatin plus irinotecan.

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 (%)	Grade (%)	Grade (%)	Grade (%)	Grade (%)	Grade (%)	Grade (%)	Grade (%)	
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	20 ^c	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 ^a	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%)		

^aIncidence of grade 3 or 4 toxicity significantly ($P < 0.05$) lower than that with IP.

^bIncidence of grade 3 or 4 toxicity significantly ($P < 0.05$) higher than that with IP.

^cIncidence of grade 2 or worse toxicity is significantly ($P < 0.05$) lower than that with IP.

^dIncidence 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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Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702

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We compared the efficacy and the safety of a carboplatin plus etoposide regimen (CE) vs split doses of cisplatin plus etoposide (SPE) in elderly or poor-risk patients with extensive disease small-cell lung cancer (ED-SCLC). Eligibility criteria included: untreated ED-SCLC; age ≥ 70 and performance status 0–2, or age < 70 and PS 3. The CE arm received carboplatin area under the curve of five intravenously (IV) on day 1 and etoposide 80 mg m^{-2} IV on days 1–3. The SPE arm received cisplatin 25 mg m^{-2} IV on days 1–3 and etoposide 80 mg m^{-2} IV on days 1–3. Both regimens were given with granulocyte colony-stimulating factor support in a 21–28 day cycle for four courses. A total of 220 patients were randomised. Median age was 74 years and 74% had a PS of 0 or 1. Major grade 3–4 toxicities were (%CE/%SPE): leucopenia 54/51, neutropenia 95/90, thrombocytopenia 56/16, infection 7/6. There was no significant difference (CE/SPE) in the response rate (73/73%) and overall survival (median 10.6/9.9 mo; $P = 0.54$). Palliation scores were very similar between the arms. Although the SPE regimen is still considered to be the standard treatment in elderly or poor-risk patients with ED-SCLC, the CE regimen can be an alternative for this population considering the risk–benefit balance.

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Approximately half of patients with small-cell lung cancer (SCLC) are older than 70 years, and the proportion of elderly SCLC patients is continuously increasing in Japan (Morita, 2002). However, since many investigators have arbitrarily excluded elderly patients from clinical trials, no standard chemotherapeutic regimen has been established for elderly patients with SCLC. The Japan Clinical Oncology Group (JCOG) has reported that carboplatin plus etoposide (CE) is an active and less toxic regimen in elderly patients with SCLC (Okamoto *et al*, 1999). However, other clinical trials have indicated that the combination chemotherapy of reduced (Souhami *et al*, 1997) or split doses of cisplatin plus etoposide (SPE) (Murray *et al*, 1998; Westeel *et al*, 1998) can be safely and effectively administered in elderly or poor-risk patients with SCLC. Therefore, we conducted a phase III trial comparing CE with SPE in elderly or poor-risk patients with SCLC. Although elderly is not the same as poor-risk, many clinical trials for the elderly have included both types of patients. Therefore, we

decided to include both elderly and poor-risk patients with SCLC at the time of proposal for this phase III trial.

PATIENTS AND METHODS

Patient selection

Eligibility criteria included patients with histologically or cytologically confirmed SCLC who were ≥ 70 years of age and had an Eastern Cooperative Oncology Group performance status (PS) of 0–2, or who were < 70 years in age and had a PS of 3. Additional criteria consisted of extensive disease (ED), chemotherapy-naïve, evaluable or measurable disease, expected survival ≥ 2 months, adequate organ functions (leucocyte count $\geq 4000 \text{ mm}^{-3}$, platelet count $\geq 100000 \text{ mm}^{-3}$, haemoglobin level $\geq 9.0 \text{ g dl}^{-1}$, AST/ALT $\leq 2 \times$ upper limit of normal range, total bilirubin $\leq 1.5 \text{ mg dl}^{-1}$, creatinine $\leq 1.5 \text{ mg dl}^{-1}$, 24-h creatinine clearance (Ccr) $\geq 50 \text{ ml min}^{-1}$, and PaO₂ $\geq 60 \text{ mmHg}$), no symptomatic pericardial or pleural effusion requiring drainage, no active concomitant malignancy, no senile dementia, and written informed consent. Exclusion criteria included brain metastases requiring radiotherapy, superior vena cava (SVC) syndrome requiring radiotherapy, serious medical or psychiatric illness, or pregnancy or lactation. Staging procedures included chest X-ray, computed tomography (CT) scan of the chest, CT scan or magnetic resonance

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imaging (MRI) of the brain, CT scan or ultrasound of the abdomen, isotope bone scanning, and bone marrow aspiration or biopsy.

Treatment protocol

Patients were randomised to either the CE arm or the SPE arm. The CE regimen consisted of carboplatin area under the curve (AUC) of five intravenously (IV) on day 1 and etoposide 80 mg m⁻² IV on days 1, 2, and 3. The SPE regimen consisted of cisplatin 25 mg m⁻² IV on days 1, 2, and 3 and etoposide 80 mg m⁻² IV on days 1, 2, and 3. Cycles were repeated every 3–4 weeks for up to four courses. In our previous phase II study using the CE regimen for elderly patients with SCLC, carboplatin AUC of 5 on day 1 and etoposide 100 mg m⁻² on days 1, 2, and 3 were administered every 4 weeks (Okamoto *et al*, 1999). However, because grade 3 or 4 neutropenia occurred in 91% of the patients, in the current phase III trial we decided to reduce the etoposide dosage to 80 mg m⁻² on days 1, 2, and 3, and repeat the cycle every 3–4 weeks instead of every 4 weeks. Twenty-four-hour Cr was substituted for glomerular filtration rate (GFR) in Calvert's formula. Antiemetic prophylaxis with 5-HT₃ antagonists plus dexamethasone was used at the treating physician's discretion. According to the Japanese approved guideline, prophylactic use of recombinant human granulocyte colony-stimulating factor (G-CSF) was recommended for daily administration after day 4 until the leucocyte (neutrophil) count exceeded 10 000 (5000) mm⁻³. If the leucocyte (neutrophil) count decreased to less than 3000 (1500) mm⁻³, then G-CSF was restarted. However, the actual use of G-CSF was left at the discretion of the treating physician. Subsequent courses of chemotherapy were initiated when leucocyte count ≥ 3000 mm⁻³; platelet count ≥ 75 000 mm⁻³; Cr ≤ 1.5 mg dl⁻¹; AST/ALT ≤ 2.5 × upper limit of normal range; and either PS ≤ 2 and age ≥ 70 years, or PS ≤ 3 and age < 70 years were satisfied both after day 21 and two or more days after the discontinuation of G-CSF. If the above criteria were not satisfied by the first day of the next course, treatment was withheld until full recovery. If more than 6 weeks passed from day 1 of the last course, the patient was removed from protocol treatment. Dose modifications were made based only on grade 4 haematologic toxicities. If grade 4 leucopenia or neutropenia lasting 4 days or more was present, or grade 4 thrombocytopenia occurred, the doses for the next course were carboplatin AUC of 4 on day 1, cisplatin 20 mg m⁻² for 3 days, and etoposide 60 mg m⁻² for 3 days. If the same haematologic toxicity was observed after dose reduction, the patient was removed from protocol treatment. If grade 3 or 4 non-haematologic toxicities, except for nausea/vomiting and hyponatraemia, occurred, the patient was removed from protocol treatment even if the toxicities improved thereafter.

Responders after four courses were not allowed to receive further chemotherapy until progressive disease (PD) developed. Although post-protocol treatment was left at the discretion of the physician, crossover treatment was prohibited.

Evaluation

Tumour responses were evaluated according to World Health Organization criteria (World Health Organization, 1979). Toxicities were evaluated according to JCOG Toxicity Criteria (Tobinai *et al*, 1993), which are similar to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC ver 1) for the grading of toxicities.

Palliation score

Study-specific eight-item palliation scores were completed by patients before treatment and 3 weeks after the third course of chemotherapy. The attending physicians were not allowed to complete the scores. The items consisted of cough, pain, anorexia, shortness of breath, well-being, nausea, diarrhoea or constipation, and sleep. The items were scored as not at all present (0), a little

(1), moderate (2), and very much (3). The sum of the total score for all eight items was compared between the baseline and post-treatment assessments. If the post-treatment score was below the baseline score, the palliation score for that patient was judged as having shown improvement.

Study design and statistics

This trial was designed as a multicentre, prospective, randomised phase III trial. The study protocol was approved by the Clinical Trial Review Committee of JCOG and the institutional review board of each participating institution before the initiation of the study. The primary endpoint was overall survival (OS). In this study, the experimental arm was the CE arm and the control was the SPE arm. The MST of our previous phase II trial for elderly patients with extensive disease small-cell lung cancer (ED-SCLC) using the CE regimen was 10.1 months. The MST of the SPE regimen for a similar population was not available at the time of the study proposal. Although Westeel and co-workers in 1998 and Murray and co-workers in 1998 reported an excellent MST of SPE plus concurrent chest radiotherapy for elderly or frail patients with limited disease (LD)-SCLC, an MST of the SPE regimen for elderly or frail patients with ED-SCLC was not available at that time. The only data available on the CAV/PE regimen for elderly or poor-risk patients with SCLC using reduced cisplatin (60 mg m⁻² IV on day 1) were reported by Souhami and co-workers in 1997 and the MST of that study was 5.9 months. Therefore, for statistical calculations in the current phase III trial, we used the MST value of the Souhami trial for the control arm instead of the MST of the SPE regimen. In addition, an individualised AUC-based dosing strategy of carboplatin was expected to have greater efficacy and less toxicity compared with the SPE regimen at that time. This trial was designed as a superiority trial and the planned sample size was 110 patients in each arm for 80% power to detect a 0.67 hazard ratio for CE to SPE in OS at an alpha of 0.025 (one sided) (Schoenfeld and Richter, 1982). Patients were randomised to receive either CE or SPE with a minimisation method for balancing centre, PS (0–1 vs 2–3) and age (≥ 70 years vs < 70 years).

Survival distributions were compared by unstratified log-rank test. Proportion of improvement in palliation score was evaluated by Fisher's exact test. The change in each symptom score by treatment arm was evaluated by the Wilcoxon rank-sum test. The relationship between the interval of each chemotherapy course and the two regimens was evaluated by the Wilcoxon rank-sum test. Multivariate analysis was performed using Cox's proportional hazards model to evaluate the importance of seven clinically selected variables (treatment arm, PS, age, sex, lactate dehydrogenase level, alkaline phosphatase level, and leucocyte count) as prognostic factors. All *P*-values in this report are two sided, excluding *P*-values for OS and progression-free survival (PFS).

The interim analysis was performed after half of the planned number of patients had been enrolled in March 2002, with adjustment for multiplicity by the alpha-spending function (DeMets and Lan, 1994) with an O'Brien-Fleming type boundary. Because the interim analysis did not meet the prespecified stopping criteria, the study was continued and the planned accrual of 220 patients was randomised in this trial.

RESULTS

Patient characteristics

Between August 1998 and February 2004, a total of 220 patients were registered from 24 institutions. Baseline characteristics were well balanced between the arms. Median age was 74 years, 92% were 70 years or older, 88% were male, and 74% had a PS of 0 or 1 (Table 1). One patient in the CE arm was found to have LD after the completion of protocol chemotherapy due to protocol violation, and this patient was considered ineligible (Figure 1).

Delivery of treatment

Reasons for termination of treatment are listed in Figure 1, and there were no major differences between the arms. Of the patients, 63% in the CE arm and 67% in the SPE arm completed four courses, and 11% in the CE arm and 8% in the SPE arm did not complete treatment because of toxicity or complications. Treatment-related death (TRD) occurred in four patients; three patients in the CE arm and one in the SPE arm. All TRDs of patients who were ≥70 years old with a good pretreatment PS (all PS 1) were associated with neutropenic infection, which occurred after the first course of chemotherapy. Although the median interval of chemotherapy was slightly more prolonged in the CE arm than in the SPE arm, total delivered courses were similar between the arms (Table 2). One patient in the SPE arm never received chemotherapy due to the occurrence of delirium after registration. Dose reduction was more frequently observed in the CE arm than in the SPE arm: 29% vs 10%, $P < 0.01$. Course delay, G-CSF delivery and total courses with G-CSF delivery were similar between the arms.

Toxicity and palliation score

Toxicities are listed in Table 3. Grade 3 or 4 leucopenia and neutropenia occurred in 54 and 95% of the CE arm vs 51 and 90% of the SPE arm, respectively. Grade 3 or 4 thrombocytopenia occurred more frequently in the CE arm than in the SPE arm: 56 vs 16%, $P < 0.01$. Gastrointestinal toxicities including nausea or

vomiting and diarrhoea were mild in both arms. There were few grade 3 or 4 toxicities and no remarkable differences between the arms. Other non-haematologic toxicities were similarly distributed between the arms. Grade 3–4 hyponatraemia, mainly caused by syndrome of inappropriate antidiuretic hormone (SIADH) secretion, occurred in 14–16% of the patients. More importantly, thrombocytopenia occurred more frequently in the CE arm, but none of the patients in either arm showed grade 3 or 4 bleeding. Only one patient in the CE arm showed grade 2 bleeding. Because no grading of febrile neutropenia was listed in JCOG toxicity criteria, the rate of the toxicity was not investigated in this study.

Baseline and post-treatment palliation scores were evaluated in 220/220 (100%) and 208/220 (95%) patients, respectively. We handled missing values by imputing the worst score. Improvement was achieved in 69 (63%) patients in the CE arm vs 61 (56%) patients in the SPE arm, although the difference was not statistically significant ($P = 0.34$). Similarly, there were no statistical differences in the change of each symptom score between the arms (Table 4).

Objective tumour response, PFS and OS

The objective response rate of 73% was quite similar between the arms. Five CRs and 75 PRs were observed in each arm (Table 5). Progression-free survival curves and OS curves are shown in Figure 2A and B. Ninety-seven percent of the patients had progressed or died at the time of final analysis. Progression-free survival was quite similar between the arms ($P = 0.20$, one sided).

Table 1 Patient characteristics

	CE (n = 110)	SPE (n = 110)	P-value
Age (years)			
Median (range)	74 (56–86)	73.5 (55–85)	0.34
≥70 years old (%)	102 (93)	100 (91)	0.81
Sex (male/female)	95/15	98/12	0.68
ECOG PS, 0–1/2/3	81/2/1/8	81/19/1/0	0.80
≥5% weight loss	26	38	0.18
LN metastasis			
Contralateral mediastinum	71	59	0.13
Supraclavicular	89	79	0.15
Distant metastasis			
Liver	30	30	1.0
Lung	31	30	1.0
Brain	18	18	1.0
Bone	25	17	0.23
Adrenal	13	7	0.24
Bone marrow	12	12	1.0

CE, carboplatin plus etoposide; ECOG, Eastern Cooperative Oncology Group; LN, lymph node; PS, performance status; SPE, split doses of cisplatin plus etoposide.

Table 2 Compliance and drug delivery

	CE (n = 110)	SPE (n = 109*)	P-value
Median interval of each chemotherapy (days) (range)			
1–2	27 (14–35)	23 (20–37)	0.02 ^b
2–3	25 (21–56)	22 (20–35)	0.07 ^b
3–4	27 (21–36)	24 (21–38)	0.05 ^b
Total delivered courses/projected courses	353/440 (80%)	360/436 (83%)	
Dose reduction	32 (29%)	11 (10%)	<0.01 ^c
Course delay	45 (41%)	40 (37%)	0.58 ^c
G-CSF delivery	81 (74%)	84 (77%)	0.64 ^c
No. of courses with G-CSF delivery/number of total courses	183/354 (52%)	203/362 (56%)	

CE, carboplatin plus etoposide; G-CSF, granulocyte colony-stimulating factor; SPE, split doses of cisplatin plus etoposide. *One patient never received chemotherapy due to delirium after registration. ^bWilcoxon rank-sum test. ^cFisher's exact test.

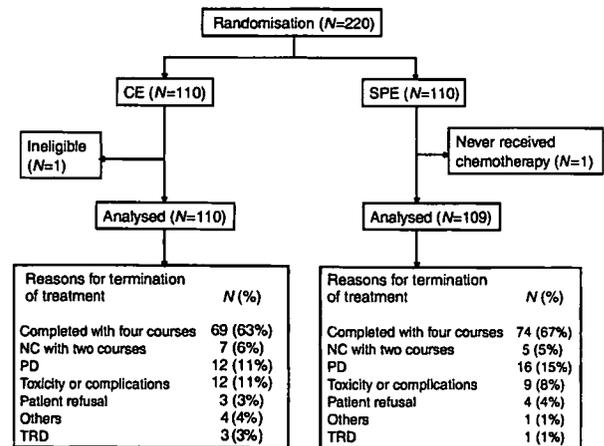


Figure 1 Flow diagram of randomised phase III trial of CE vs SPE in elderly or poor-risk patients with extensive disease SCLC.

Table 3 Toxicities (JCOG Toxicity Criteria, Worst Grade of Any Course)

Toxicity	CE					SPE					P-value
						Grade					
	1	2	3	4	3+4 (%)	1	2	3	4	3+4 (%)	
Haematologic											
Leucopenia	5	45	46	13	(54)	8	43	49	7	(51)	0.79
Neutropenia	0	5	46	58	(95)	4	7	41	57	(90)	0.22
Anaemia	9	58	32	—	(29)	20	45	27	—	(25)	0.54
Thrombocytopenia	20	18	29	32	(56)	16	15	12	5	(16)	<.01
Non-haematologic											
Nausea/vomiting	40	24	2	—	(2)	46	28	3	—	(3)	0.68
Diarrhoea	8	9	1	0	(1)	11	3	1	0	(1)	1.0
Bilirubin	—	31	0	0	(0)	—	16	1	0	(1)	0.50
AST	47	9	3	0	(3)	30	8	6	0	(6)	0.33
ALT	40	9	2	0	(2)	38	8	4	0	(4)	0.45
Creatinine	10	2	0	0	(0)	27	3	1	0	(1)	0.50
Hyponatraemia	38	11	7	11	(16)	46	20	6	9	(14)	0.58
PaO ₂	39	21	7	1	(10)	44	23	2	1	(4)	0.22
Fever	15	15	0	0	(0)	21	16	0	0	(0)	—
Infection	12	15	5	3	(7)	16	7	5	1	(6)	0.78
Bleeding	8	1	0	0	(0)	4	0	0	0	(0)	—
Neurologic-sensory	2	1	0	—	(0)	3	2	0	—	(0)	—
Alopecia	67	22	—	—	—	66	15	—	—	—	—

CE, carboplatin plus etoposide; JCOG, Japan Clinical Oncology Group; PaO₂, partial pressure of oxygen; SPE, split doses of cisplatin plus etoposide.

Table 4 Palliation score

Symptom	CE		SPE		P ^a
	Change from baseline		Change from baseline		
	Mean (s.d.)	Median (range)	Mean (s.d.)	Median (range)	
Cough	-0.38 (1.16)	0 (-3 to 3)	-0.54 (1.06)	0 (-3 to 3)	0.51
Pain	-0.19 (1.00)	0 (-3 to 3)	-0.19 (0.96)	0 (-3 to 3)	0.96
Anorexia	-0.07 (1.16)	0 (-3 to 3)	0.08 (1.22)	0 (-3 to 3)	0.37
Shortness of breath	-0.05 (1.02)	0 (-2 to 3)	-0.31 (0.95)	0 (-3 to 3)	0.12
Well-being	-0.15 (1.13)	0 (-3 to 3)	-0.02 (1.14)	0 (-3 to 3)	0.48
Nausea	0.16 (0.84)	0 (-2 to 3)	0.26 (0.80)	0 (-1 to 3)	0.21
Diarrhoea or constipation	0.05 (1.07)	0 (-3 to 3)	0.04 (0.99)	0 (-3 to 3)	0.69
Sleep	-0.15 (1.08)	0 (-3 to 3)	-0.04 (0.89)	0 (-3 to 2)	0.10
Total	-0.80 (6.04)	-2 (-12 to 22)	-0.71 (5.35)	-1 (-15 to 21)	0.32

CE, carboplatin plus etoposide; s.d., standard deviation; SPE, split doses of cisplatin plus etoposide. ^aWilcoxon rank-sum test.

The MST was 5.2 months in the CE arm vs 4.7 months in the SPE arm. OS was very similar between the arms ($P=0.54$, one sided). The MST and 1-year survival rate was 10.6 months and 41% in the CE arm vs 9.9 months and 35% in the SPE arm.

Second-line chemotherapy

According to an *ad-hoc* survey (not pre-specified in the protocol), 130 (59%) patients (68 (62%) patients in the CE arm and 62 (56%) in the SPE arm) received second-line chemotherapy after relapse and the regimens were almost equally distributed between the arms. The same regimen as the initial chemotherapy, platinum-based combinations, and irinotecan regimens with or without other agents were administered in 17 (15%), 48 (44%), and 40 (36%) patients in the CE arm vs 10 (9%), 44 (40%), and 40 (36%) in

Table 5 Therapeutic response (WHO)

	CE	SPE	Total
CR	5	5	10
PR	75	75	150
NC	17	11	28
PD	11	16	27
NE	2	3	5
Total	110	110	220
Response rate	73%	73%	
95% CI	63-81%	63-81%	

CE, carboplatin plus etoposide; CI, confidence interval; CR, complete response; NC, no change; NE, not evaluable; PD, progressive disease; PR, partial response; SPE, split doses of cisplatin plus etoposide; WHO, World Health Organization.

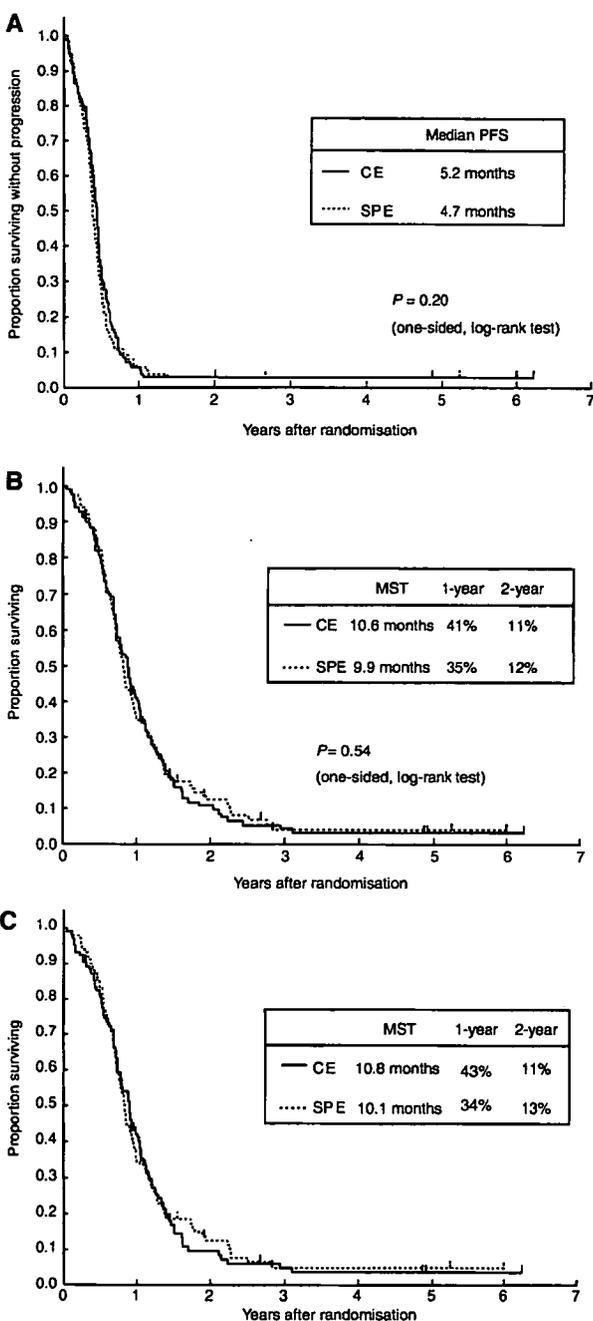


Figure 2 (A) PFS curves ($n=220$). (B) OS curves ($n=220$). (C) Survival curves of the patients ≥ 70 years of age with a PS of 0–2 ($n=202$).

the SPE arm. Other chemotherapy regimens included topotecan monotherapy, amrubicin monotherapy, or other regimens.

Subset analysis and multivariate analysis

Subset analysis was performed according to PS and age (Table 6). There were no differences in OS between the arms in any subset; thus, an interaction between treatment and PS is unlikely. The survival curves of the patients ≥ 70 years of age with a PS of 0–2 are shown in Figure 2C, and the survival curves were very

Table 6 Subset analysis – overall survival

Subgroup	Number of patients (%)	MST (months)	
		CE	SPE
PS 0–1	162 (74)	10.9	10.1
PS 2–3	58 (26)	8.3	8.1
<70 years and PS 3	18 (8)	7.1	6.9
≥ 70 years and PS 0–2	202 (92)	10.8	10.0

CE, carboplatin plus etoposide; MST, median survival time; PS, performance status; SPE, split doses of cisplatin plus etoposide.

Table 7 Multivariate analysis with baseline prognostic factors

Variables	P-value	Hazard ratio	95% CI
Treatment arm (CE vs. SPE)	0.99	0.99	0.75–1.33
Alkaline phosphatase level (normal vs abnormal)	0.97	0.99	0.68–1.46
Lactate dehydrogenase level ($\geq \times 1.5$ vs $< \times 1.5$)	<0.001	1.69	1.23–2.26
Leucocyte count ($\geq 10\,000/\text{mm}^3$ vs $< 10\,000/\text{mm}^3$)	0.06	1.82	0.99–3.36
Age (≥ 75 years vs < 75 years)	0.77	1.05	0.78–1.41
PS (2–3 vs 0–1)	0.41	1.15	0.82–1.61
Sex (female vs male)	0.13	0.70	0.45–1.11

CE = carboplatin plus etoposide; SPE = split doses of cisplatin plus etoposide; PS = performance status; CI = confidence interval.

similar with that of original overall populations. Even in the multivariate analysis with seven selected baseline variables, there was no difference in OS between the arms. High lactate dehydrogenase level was most strongly associated with poor prognosis (Table 7).

DISCUSSION

Until recently, there was no standard chemotherapeutic regimen for elderly SCLC patients. Two phase III (Medical Research Council Lung Cancer Working Party, 1996; Souhami *et al*, 1997) and two randomised phase II trials (Pfeiffer *et al*, 1997; Ardizzoni *et al*, 2005) have shown that suboptimal chemotherapies, such as oral etoposide monotherapy or attenuated doses of combination chemotherapy, may lead to reduced survival in elderly or poor-risk SCLC patients when compared with standard doses of combination chemotherapies. The CE regimen, which has acceptable toxicities and reproducible efficacy, has been used in elderly or poor-risk patients with SCLC worldwide, although there have been substantial differences in toxicities and efficacy between the reported phase II trials. Four trials demonstrated both favourable toxicities and efficacy (Carney, 1995; Evans *et al*, 1995; Matsui *et al*, 1998; Okamoto *et al*, 1999) and three showed somewhat disappointing results because of suboptimal doses of oral etoposide (Larive *et al*, 2002), greater inclusion of patients with poor prognostic factors (Samantas *et al*, 1999), and deterioration of comorbidities as a result of chemotherapy (Quoix *et al*, 2001). No phase III trial evaluating the role of the CE regimen in this population has been reported until now.

This is the first phase III trial comparing carboplatin-based CE and cisplatin-based SPE regimens in elderly or poor-risk patients with ED-SCLC. In addition, this is also the largest randomised trial specifically designed for elderly or poor-risk SCLC patients. Although there was no significant difference in the palliation scores, response rate, and OS between the arms, the efficacy of

both regimens was promising, as this study included only elderly or poor-risk patients with SCLC. Most toxicities were tolerable and the treatment compliance was also favourable in both arms. Approximately two-thirds of the patients received all four cycles of treatment. The CE arm in the current trial had more pronounced thrombocytopenia, which was considered manageable because none of the patients in the CE arm showed grade 3 or 4 bleeding, and the CE arm had a slightly prolonged course interval and a slightly greater incidence of dose reduction. However, in our opinion, these toxicities are less meaningful in clinical practice. More importantly, the CE regimen does not require hydration and can be given in an outpatient setting. Based on the results of this study, many JCOG members prefer the CE regimen to the SPE regimen and consider it to be more suitable for the control arm of future phase III trials.

The MST of each regimen (10.6 months for CE vs 9.9 months for SPE) was promising considering that this study included only elderly or frail patients with ED-SCLC. However, some retrospective studies have shown that fit elderly patients who have adequate organ functions, a good PS, and no comorbidity are able to tolerate intensive chemotherapy well and show a similar therapeutic response and survival rate as younger patients (Siu *et al*, 1996; Yuen *et al*, 2000). In fact, in this trial the MST of fit elderly patients ≥ 70 years of age with a PS of 0–1 was 10.9 months for the CE arm and 10.1 months for the SPE arm. In contrast, the MST of patients with a PS of 3 was only approximately 7 months. Furthermore, the group of fit elderly patients comprised 74% of the patients in this study. Therefore, the favourable survival rates in our trial may be attributable to patient selection. In other words, one limitation of this study is that the results of this trial cannot be extrapolated to frail elderly with a poor PS and/or comorbid illness because of the likelihood of greater inclusion of fit elderly patients in this trial.

Although the total dose in both the CE and SPE arms was slightly lower than the standard regimen, 92% of the patients showed grade 3 or 4 neutropenia, and dose reduction and course delay occurred frequently. However, the MST of both regimens was comparable with that of non-elderly or non-selected patients with ED-SCLC in historical reports (Noda *et al*, 2002; Niell *et al*, 2005). These findings suggest that both regimens are not suboptimal, but are near-full and effective doses for elderly or poor-risk patients with ED-SCLC. The CE arm in the current trial had a slightly prolonged course interval and a slightly greater incidence of dose reduction when compared to the SPE regimen. However, 95% of the patients showed grade 3 or 4 neutropenia and 56% showed grade 3 or 4 thrombocytopenia. Therefore, we believe that the dose escalation of the CE regimen may be difficult in this trial.

It remains unclear whether the elderly are able to tolerate a single modest dose of cisplatin (60–80 mg m⁻² IV) on day 1. We feel that a fit elderly person who passes strict eligibility criteria can receive a modest dose of cisplatin IV on day 1. However, the more common situation is of elderly patients who have comorbidity and a poor PS, and cannot tolerate a standard single dose of cisplatin. Westeel *et al* (1998) and Murray *et al* (1998) reported that split doses of cisplatin were safely and effectively administered in elderly or frail patients with LD-SCLC. The SPE regimen appeared to be an appropriate treatment for elderly patients with SCLC who cannot tolerate a standard single dose of cisplatin. However, it remains unclear whether fit elderly patients in our trial can tolerate a standard single dose of cisplatin, and if so, it also remains unclear whether fit elderly patients who receive a standard single dose of cisplatin are able to achieve a more improved survival than those who receive SPE. Unfortunately, no randomised study comparing a single standard dose of cisplatin with SPE has been reported in fit elderly patients with SCLC.

There are some problems with the design in this study. The hypothesis was that carboplatin would improve survival, and

the design of the trial was a superiority design with survival as the primary end point. However, this hypothesis was based on two possible misconceptions. First, carboplatin could be better dosed and might be more efficacious than cisplatin in SCLC. Unfortunately, this hypothesis could not be sustained on the basis of the available literatures. A number of clinical trials have indicated that carboplatin-based combination chemotherapy has a similar or slightly reduced efficacy compared with cisplatin-based combination chemotherapy against various tumours (Go and Adjei, 1999; Hotta *et al*, 2004). Therefore, our trial should have been designed as a non-inferiority trial. However, if this trial were planned as a non-inferiority trial, a total sample size would be about 500 to 1000 patients, with equal expected survival and a non-inferiority margin for hazard ratio ranging from 1.2 to 1.3. Second, the cisplatin dose in the control arm was an attenuated dose. Souhami *et al* (1997) used reduced dose of cisplatin (60 mg m⁻² IV on day 1) and Murray *et al* (1998) used a single course of a split cisplatin dose in their studies. These regimens were completely different from the control arm in the present study. A standard dose of cisplatin given in 3 days is the best way of giving standard cisplatin (30 mg m⁻² IV on days 1–3) with etoposide (130 mg m⁻² IV on days 1–3), according to the North Central Cancer Treatment Group (Maksmiuk *et al*, 1994). Had standard SPE been used for the control arm, better survival might have been achieved with increased toxicities. Another problem with the design was the inclusion of patients with a PS of 3, even if they were less than 70 years old. This made the target population heterogeneous. The number of such patients actually recruited was quite small, so emphasising the inappropriateness of their inclusion. A further limitation of this study may be a long accrual period of five-and-a-half years. Because our oncologists might have been afraid of the risk of TRD or increased toxicities in frail elderly with a poor PS and/or comorbid illness, more fit elderly patients were selectively registered and consequently the accrual rate was very slow.

In our trial, although both regimens were well-tolerated and efficacy was promising, over 90% of the patients in both arms showed grade 3 or 4 neutropenia, which may be justified and acceptable for a clinical trial involving elderly or poor risk patients with ED-SCLC, because only 6% of the patients showed grade 3 or 4 infection and TRD occurred in only four (1.8%) patients. Because all TRD occurred after the first course of chemotherapy, careful monitoring and management is necessary, particularly in the first course, if CE or SPE are administered to elderly or frail patients. Several retrospective analyses (Findlay *et al*, 1991; Radford *et al*, 1992) and a prospective study (Timmer-Bonte *et al*, 2005) have shown that standard-dose chemotherapy without G-CSF support causes more risk of early death and sepsis in the older population. Moreover, the American Society of Clinical Oncology (ASCO) guideline recommends the use of prophylactic G-CSF in patients at higher risk for chemotherapy-induced infection, such as those having a poor PS, older age, or comorbid illness (Smith *et al*, 2006). In this trial, the prophylactic use of G-CSF was recommended, but the actual use was left to the discretion of the treating physician because the use of G-CSF leads to increased drug cost. Although G-CSF was administered in only 54% of the total courses, we believe that the prophylactic use of G-CSF with CE regimen should be recommended in a new trial or clinical practice.

In conclusion, although the SPE regimen is still considered to be the standard treatment for elderly or poor-risk patients with ED-SCLC, the CE regimen can be an alternative for this population considering the risk-benefit balance. Based on the results of our trial, a phase III trial of the CE regimen vs amrubicin monotherapy, supported by a pharmaceutical company, is now ongoing in elderly patients with ED-SCLC in Japan, and a comparative trial of the CE regimen vs carboplatin plus irinotecan regimen (Okamoto *et al*, 2006) is being discussed for a future trial in our group.

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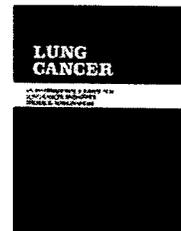
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Clinical Studies

Appendix

This study was coordinated by the Japan Clinical Oncology Group (N Saijo, Chairperson) and was performed with the cooperation of the following institutions and investigators: Tohigi Cancer Center Hospital, Tohigi (K Mori, M Noda, T Kondo, and Y Kamiyama); National Nishi-Gunma Hospital, Gunma (S Tsuchiya, Y Koike, K Satoh, A Tohi, and K Kaira); Gunma Cancer Center Hospital, Gunma (K Minato); Saitama Cancer Center Hospital, Saitama (H Sakai, K Kobayashi, and R Kuroki); National Cancer Center, Central Hospital, Tokyo (T Tamura, Y Ohe, H Kunitoh, I Sekine, H Nokihara, and H Murakami); National Cancer Center Hospital East, Chiba (R Kakinuma, K Kubota, H Ohmatsu, K Gotoh, and S Niho); National International Medical Center, Tokyo (Y Takeda, S Izumi, A Kawana, M Kamimura, and M Iikura); Toranomon Hospital, Tokyo (K Kishi, and M Kawabata); Kanagawa Cancer Center Hospital, Kanagawa (K Yamada, I Nomura, F Oshita, and M Ikehara), Yokohama Municipal Citizen's Hospital, Kanagawa (K Watanabe, H Kunikane, H Okamoto, A Nagatomo, and H Aono); Niigata Cancer Center Hospital, Niigata (A Yokoyama, H Tsukada, M Makino, T Shinbo, S Kinebuchi, J Tanaka, M Tango, and

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Randomized trial of drip infusion versus bolus injection of vinorelbine for the control of local venous toxicity

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KEYWORDS

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Toxicity;
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Randomized trial

Summary Vinorelbine is a moderate vesicant that is well known to cause local venous toxicity such as drug induced-phlebitis. We conducted a prospective randomized trial to determine whether a 1-min bolus injection (1 min bolus) of vinorelbine reduced the incidence of local venous toxicity compared with a 6-min drip infusion (6 min infusion). Non-small cell lung cancer patients who were to receive chemotherapy containing vinorelbine were randomly assigned to receive either 6 min infusion or 1 min bolus of the drug. All infusions were administered through a peripheral vein. Local venous toxicity was evaluated at each infusion up to two cycles. Eighty-three patients were randomized into the study and 81 of them assessable for analysis. One hundred thirty-eight infusions to 40 patients in 6 min infusion and 135 infusions to 41 patients in 1 min bolus were delivered. Vinorelbine induced-local venous toxicity was observed in 33% of patients in 6 min infusion and 24% in 1 min bolus. There was no statistically significant difference between the two arms ($P=0.41$). The incidence of local venous toxicity per infusions was 16% (22 of 138 infusions) in 6 min infusion and 11% (15 of 135 infusions) in 1 min bolus ($P=0.47$). No severe local venous toxicity was seen in either arm. In this study, the administration of in 1 min bolus of vinorelbine did not significantly reduce the incidence of local venous toxicity compared with 6 min infusion. Further studies for the control of local venous toxicity of vinorelbine are warranted.

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1. Introduction

Vinorelbine is a second-generation semi-synthetic vinca alkaloid whose antitumor activity is related to its ability to depolymerize microtubules and disrupt the mitotic spindle apparatus [1]. Vinorelbine has been shown to have clearly higher activity and lower neurotoxicity than the other vinca

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alkaloids, and is currently one of the most active agents for the treatment of non-small cell lung cancer (NSCLC) or other solid tumors [2–4].

Vinorelbine is most commonly administered through a peripheral vein as drip infusion over a period of between 6 and 10 min [5]. However, vinorelbine is a moderate vesicant that is well documented to cause local venous toxicity such as drug induced-phlebitis and venous irritation, and its incidence of approximately 30% has been reported in patients who received vinorelbine via a 6–10 min drip infusion [6,7]. Although local venous toxicity is not life threatening, it can result in discomfort or pain and can be a disincentive of chemotherapy to the patients. Therefore local venous toxicity should be managed effectively to decrease patient discomfort.

Recently, a retrospective study on drug induced-phlebitis with bolus injection of vinorelbine has been reported. In the analysis of 39 patients who received the administration of bolus injection of vinorelbine, drug induced-phlebitis occurred in only 1 of 39 patients (2.6%). The results suggested that the administration of bolus injection of vinorelbine might decrease the incidence of drug induced-phlebitis when compared common drip infusion [8]. Furthermore, shortening the infusion time of vinorelbine has also been reported to reduce the incidence of drug induced-phlebitis [9], although a randomized trial evaluating the bolus injection of vinorelbine has not been performed.

We conducted a prospective randomized trial to determine whether a 1-min bolus injection (1 min bolus) of vinorelbine reduced the incidence of local venous toxicity compared with a 6-min drip infusion (6 min infusion). In addition, we assessed the incidence of acute lower back pain, which has been reported to occur in shorter time infusions of vinorelbine [10] as other toxicity.

2. Patients and methods

2.1. Patient eligibility

Patients who had histological or cytological evidence of cancer, and planned to receive vinorelbine-containing chemotherapy as peripheral infusion, were eligible for this study. The patients were required to be 20 years of age or older and have an Eastern Cooperative Oncology Group performance status (PS) of 0–2. Patients were excluded if they had previous treatment with vinorelbine, medical condition that required regular use of steroids, or were pregnant or nursing. All patients provided written informed consent before randomization for this study, and the study was approved by the institutional review board at the National Cancer Center.

2.2. Study design

This study was a randomized trial comparing 1 min bolus of vinorelbine with 6 min infusion for the control of local venous toxicity. The study was performed in the National Cancer Center Hospital East. Patients were randomly assigned to receive either 6 min infusion or 1 min bolus by a minimization method. Before randomization, patients were stratified by chemotherapy regimens (stra-

tum I: vinorelbine plus cisplatin, stratum II: vinorelbine plus gemcitabine, stratum III: vinorelbine alone) and body mass index (BMI) (stratum I: normal (BMI < 24), stratum II: high (BMI 24 or more)). We reported previously that high BMI was associated with a significant increased risk of vinorelbine irritation [6].

2.3. Treatment plan

Patients received either 6 min infusion or 1 min bolus of vinorelbine. Vinorelbine was diluted in 50 ml (6 min infusion) or 20 ml (1 min bolus) normal saline, respectively. All infusions were administered through a peripheral vein and followed by flushing the vein with approximately 200 ml of fluid. The administration of other drugs for the prevention of local venous toxicity was not allowed. Vinorelbine-containing chemotherapy regimens consisted of vinorelbine 20–25 mg/m² on days 1 and 8 plus cisplatin 80 mg/m² on day 1 every 3 weeks, vinorelbine 20–25 mg/m² plus gemcitabine 1000 mg/m² on days 1 and 8 every 3 weeks, or vinorelbine 20–25 mg/m² alone on days 1, 8 and 15 every 4 weeks.

2.4. Outcome assessment

The primary endpoint of this study was the incidence of local venous toxicity per patient. Local venous toxicity was evaluated at each infusion up to two cycles and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 for injection site reaction by attending physician: grade 0, none; grade 1, pain, itching or erythema; grade 2, pain or swelling, with inflammation or phlebitis; and grade 3, ulceration or necrosis that is severe or prolonged or requires surgery. After the administration of vinorelbine, patients self-recorded in personal dairies symptoms of pain, itching, swelling, blister, or ulceration at injection. The patient's dairies were also used for support of diagnosis of local venous toxicity. Local venous toxicity was categorized as positive or negative, with positive defined as experience of grade 1 or more local venous toxicity at least once during treatment. The secondary endpoint of this study was the incidence of local venous toxicity per infusions and other toxicity. The incidence of acute lower back pain, which was reported to occur in shorter time infusion of vinorelbine, and hematological toxicity were mainly assessed as the other toxicity, and graded according to NCI-CTC version 2.0.

2.5. Statistical analysis

The purpose of this study was to determine whether 1 min bolus of vinorelbine reduced the incidence of local venous toxicity compared with 6 min infusion. The calculation of sample size was based on the estimated incidence of local venous toxicity per patient in the two treatment groups. On the basis of previous reports [6,8], an incidence of local venous toxicity per patients of 30% in 6 min infusion and of 5% in 1 min bolus was assumed. To demonstrate this hypothesis with an alpha of 5% and a power of 80% in a two-sided test, thirty-five patients from each group were required. A total of 80 patients were projected to be accrued. All comparisons between proportions were performed by the Chi-square test

or Fisher's exact test, as appropriate. Multivariate analysis was performed by logistic regression procedure to determine the relationship between the incidence of local venous toxicity and the clinical variables. *P* values < 0.05 were considered significant. The reported *P* values were based on two-sided tests. Statistical analysis software (StatView-J Ver.5.0, Macintosh) was used for the analyses.

3. Results

3.1. Patient characteristics

Between October 2002 and April 2003, 83 patients were enrolled and randomly assigned into the study. Baseline patient characteristics according to treatment group are shown in Table 1. The two treatment groups were well balanced in regards to age, PS, chemotherapy regimens, and BMI. All patients had advanced NSCLC and no prior chemotherapy. Two patients were not assessable for analysis because they refused to receive chemotherapy after randomization.

Treatment delivery is shown in Table 2. One hundred and thirty-eight infusions to 40 patients in 6 min infusion and 135 infusions to 41 patients in 1 min bolus were delivered. There was no significant difference between the two arms for treatment delivery of vinorelbine.

3.2. The incidence of local venous toxicity

The incidence of local venous toxicity was 33% (95% confidence interval (CI), 18.6–49.1%) in 6 min infusion (13 of the 40 patients) and 24% (95% CI, 12.4–40.3%) in 1 min bolus (10 of the 41 patients) (Fig. 1a). There was no statistically

	6 min drip infusion	1 min bolus injection
Evaluable patients	40	41
Vinorelbine infusions		
1	1	3
2	9	8
3	1	4
4	29	26
Total infusions	138	135
Vinorelbine (mg)/body		
Median (range)	39 (30–48)	40 (27–48)

significant difference between the two arms (*P*=0.41; relative risk, 0.67; 95% CI, 0.25–1.77). In 6 min infusion, grade 1 local venous toxicity was observed in 12 patients, grade 2 in 1 patient; in 1 min bolus, grade 1 local venous toxicity was observed in 8 patients, grade 2 in 2 patients. No severe local venous toxicity was seen with both arms. The incidence of local venous toxicity per infusions was 16% in 6 min infusion (22 of 138 infusions) and 11% in 1 min bolus (15 of 135 infusions) (*P*=0.47) (Fig. 1b).

The incidence of local venous toxicity according to chemotherapy regimens were 29% (18/60) in the vinorelbine plus cisplatin group, 22% (2/9) in the vinorelbine plus gemcitabine group, and 25% (1/4) in the vinorelbine alone group, respectively. The incidence of local venous toxicity in the normal BMI group was 30% compared with 24% in the high BMI group (*P*=0.77). There was no statistically significant difference among the stratified factors. We used multivariate logistic regression analysis to determine the relationship

Table 1 Baseline patients characteristics

Characteristic	6 min drip infusion (n=41)		1 min bolus injection (n=42)		<i>P</i>
	No.	%	No.	%	
Age (years)					
Median	65		65		0.37
Range	42–76		49–78		
Sex					
Male	29	71	36	86	0.10
Female	12	29	6	14	
ECOG performance status					
0/1	7/29	88	11/28	93	0.48
2	5	12	3	7	
Chemotherapy regimen					
Vinorelbine/cisplatin	35	85	35	83	0.95
Vinorelbine/gemcitabine	4	10	5	12	
Vinorelbine alone	2	5	2	5	
Body mass index					
Median (range)		21.7 (13.5–34.2)		21.2 (14.7–29.9)	0.79
Normal ≤ 24	31	76	31	74	
High > 24	10	24	11	26	

ECOG, Eastern Cooperative Oncology Group.

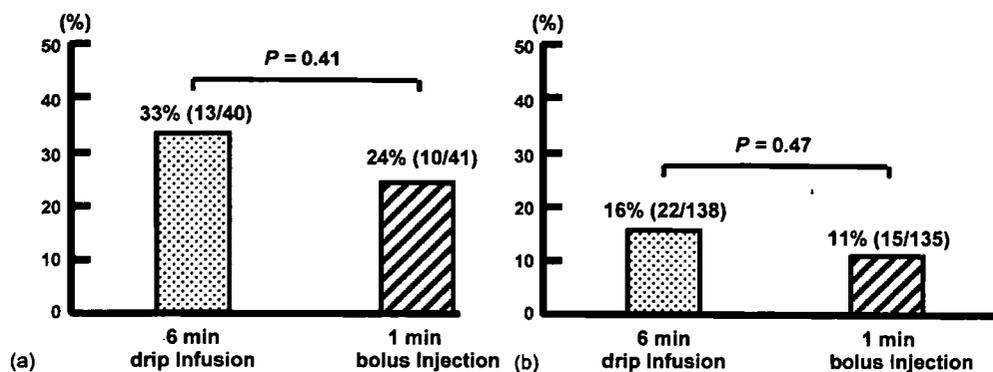


Fig. 1 The incidence of local venous toxicity: (a) per patient, (b) per infusions.

between local venous toxicity and the clinical variables (sex, age, chemotherapeutic regimen, BMI, the dose of VNR, and treatment arm). No significant correlations between the incidence of local venous toxicity and the clinical variables were found.

According to the patient's self-recorded diary, 43% (17/40) of patients in 6 min infusion had at least one symptom at injection site and 34% (14/41) of patients in 1 min bolus ($P=0.43$).

3.3. Other toxicity

Acute lower back pain (>grade 1) was observed in 8% of 6 min infusion, and in 7% of 1 min bolus. There was no statistically significant difference between the two arms ($P>0.99$). Grade 3/4 neutropenia and thrombocytopenia occurred with similar frequency in both arms.

4. Discussion

Local venous toxicity such as drug induced-phlebitis is one of the discomforting toxicities for patients in cancer chemotherapy. Vinorelbine is generally well tolerated and can be administered safely in an outpatient setting; however, it is a moderate vesicant with the potential to cause local venous toxicity. In our study, the incidence of local venous toxicity with the 6-min drip infusion of vinorelbine, which was used as control arm, was 33%, a similar frequency as found in past reports [6,7].

This is the first randomized study that evaluated the incidence of local venous toxicity with the bolus injection of vinorelbine. In this study, the administration of 1 min bolus of vinorelbine did not significantly reduce the incidence of local venous toxicity compared with 6 min infusion. The 24% rate of local venous toxicity with 1 min bolus of vinorelbine, which was observed in our study, was higher than anticipated in the study hypothesis. We speculate that our study hypothesis overestimated the incidence of local venous toxicity with 1 min bolus of vinorelbine because the previous reference reports were not prospective randomized studies [7,8]. Indeed, our study indicated that the administration of 1 min bolus of vinorelbine resulted in a non-statistically significant 27% reduction in rate of local venous toxicity compared with the 33% rate of 6 min infusion. We think that our

study might have no under power to detect a clinically significant difference between the two treatment groups. In our study, an overall incidence of local venous toxicity was 28% although no severe local venous toxicity was seen. If a patient with only poor peripheral venous access receives the administration of vinorelbine, the use of implantable central venous access device should be considered. Moreover, the administration of 1 min bolus of vinorelbine has not been associated with an increased risk of acute lower back pain, which was previously reported to occur in shorter time infusions of vinorelbine [10]. Hematologic toxicity such as neutropenia and thrombocytopenia were also equivalent in both arms. In addition, we examined the clinical risk factors related to local venous toxicity of vinorelbine, but unfortunately there was no significant clinical risk factor in this study.

Two other randomized studies have been performed for the control of local venous toxicity of vinorelbine. Lazano et al. [9] compared the use of heparin-containing solution as anti-thrombotic effect [11] with 10-min infusion of vinorelbine. In their study, a population of 23 patients was randomized to arm A, in which vinorelbine plus 5000 U of heparin was diluted in 500 ml of normal saline and infused over 2 h, or arm B, in which vinorelbine was diluted in 50 ml of normal saline and infused over 10 min. Arm A with heparin was found to be inferior to arm B in terms of pain control at the injection site. Fasce et al evaluated the influence of infusion time of vinorelbine on local venous toxicity in a randomized cross-over trial [10]. Forty-eight patients with solid tumors were randomized to 6-min infusion or 20-min infusion of vinorelbine. Local venous toxicity was recorded in 23 patients (48%) in the 6-min infusion group, and in 26 patients (56%) in the 20-min infusion group, respectively. On the basis of their results, we used the administration of 6 min infusion of vinorelbine as the control arm in this study. The use of defibrotide [12,13] as another anti-thrombotic drug, or cimetidine [14], which was reported to inhibit histamine actions in endothelial cells by vinorelbine [15], have been investigated in an attempt to reduce the incidence of local venous toxicity of vinorelbine. However, there have been no randomized controlled trials to verify the benefit of these methods, and thus a randomized controlled study is needed to draw definitive conclusions about their efficacy.

In conclusion, our findings indicated that the incidence of local venous toxicity with 1 min bolus of vinorelbine was

higher than previously reported. In our study, the administration of 1 min bolus of vinorelbine did not significantly reduce the incidence of local venous toxicity compared with 6 min infusion. Further studies for the control of local venous toxicity of vinorelbine are warranted.

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