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

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

introduction

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

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

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

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

patients and methods

patient selection

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

treatment schedule

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

response and toxicity evaluation

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

quality of life assessment

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

statistical analysis and monitoring

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

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

results

patient characteristics

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

objective tumor response and response duration

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

Table 1. Patient characteristics and treatment delivery

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

PS, performance status; SD, standard deviation.

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

	N	Median survival, months	1-year survival (%)	Difference 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 (n = 45)
Carboplatin + paclitaxel	145	12.3	51.0	−8.2% (95% CI −19.6% to 3.3%)	25.5	4.5 (P = 0.355)[a]	3.2 (P = 0.282)[a]	32.4 (P = 0.801)[b]	4.0 (n = 47)
Cisplatin + gemcitabine	146	14.0	59.6	0.4% (95% CI −10.9% to11.7%)	31.5	4.0 (P = 0.170)[a]	3.2 (P = 0.567)[a]	30.1 (P = 0.868)[b]	3.5 (n = 44)
Cisplatin + vinorelbine	145	11.4	48.3	−10.9% (95% CI −22.3% to 0.5%)	21.4	4.1 (P = 0.133)[a]	3.0 (P = 0.091)[a]	33.1 (P = 0.706)[b]	3.4 (n = 48)

[a]Compared with IP by the generalized Wilcoxon test.
[b]Compared with IP by the χ^2 test.
CI, confidence interval; IP, cisplatin plus irinotecan; TTP, time to progressive disease; TTTF, time to treatment failure.

OS, TTP disease, and TTTF

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

hematologic and non-hematologic toxicity

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

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

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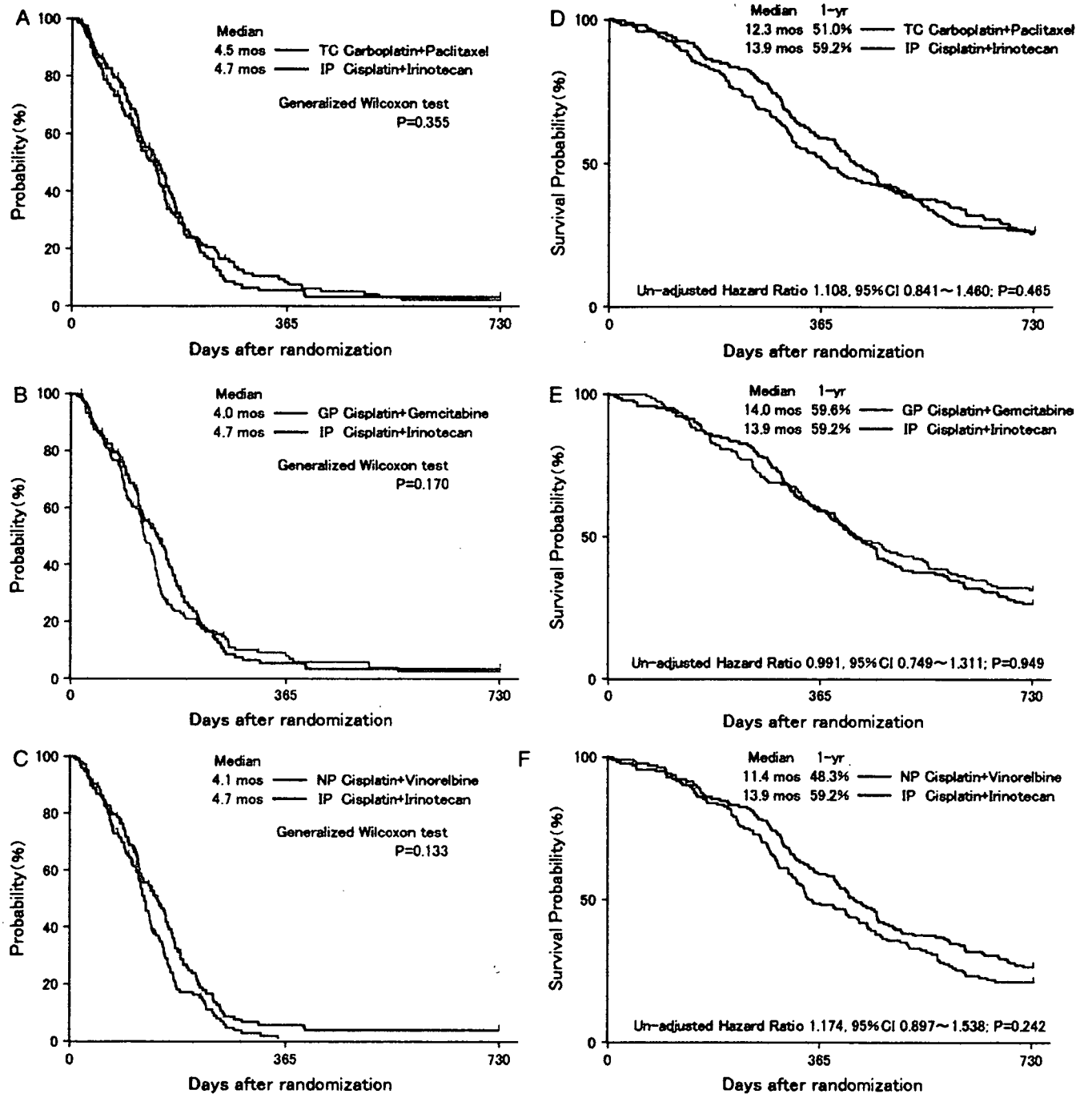

Figure 1. Overall survival (OS) and time to progressive (TTP) disease. TTP and OS in the carboplatin plus paclitaxel (TC) (A, D), cisplatin plus gemcitabine (GP) (B, E), and cisplatin plus vinorelbine (NP) (C, F) were not statistically significantly different from the values in the cisplatin plus irinotecan.

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 = 154)			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[a]	2[a]	25	51[b]	16[b]
Neutrophils	11	39	45	5	19	69	21	40	23[a]	5	16	72
Hemoglobin	42	24	7	42	13[a]	2[a]	44	22	5	43	25	5
Platelets	6	5	1	9	11	0	22	35[b]	0[b]	3	1[a]	0[a]
Febrile neutropenia	–	14	0	–	18	0	–	2[a]	0[a]	–	18	0
Nausea	32	29	–	14[c]	11[c]	–	35	23	–	33[c]	14[c]	–
Vomiting	38	13	0	17[c]	5[c]	0[c]	34	14	0	29[c]	7[c]	0[c]
Anorexia	30	33	2	15[c]	17[c]	1[c]	31	26	1	29[c]	20c	1[c]
Fatigue	27	12	1	26	2	1	17[c]	3[c]	0[c]	23[c]	3[c]	0[c]
Diarrhea	33	15	1	4[c]	3[c]	0[c]	7[c]	2[c]	0[c]	8[c]	4[c]	0[c]
Constipation	27	7	0	30	8	0	33	9	0	40[d]	14[d]	0[d]
Neuropathy, motor	1	0	0	1	1	1	0	0	0	0	0	0
Neuropathy, sensory	1	0	0	14[d]	3[d]	0[d]	0	0	0	0	0	0
Alopecia	31	–	–	45[d]	–	–	15[c]	–	–	9[c]	–	–
Arthralgia	2	0	0	20[d]	2[d]	0[d]	0	0	0	1	0	0
Myalgia	1	0	0	16[d]	2[d]	0[d]	0	0	0	1	1	0
Injection site reaction	5	0	–	5	0	–	5	0	–	27[d]	0[d]	–
Pneumonitis	0	1	1	0	1	0	0	0	0	0	1	0
Creatinine	8	1	0	2[c]	0[c]	0[c]	7	0	0	8	1	0
AST	7	1	1	5	1	0	6	3	0	1	3	0
Fever	2	0	0	5	1	0	1	0	0	1	0	0
Treatment-related death	3 (2.0%)			1 (0.7%)			0			1 (0.7%)		

[a]Incidence of grade 3 or 4 toxicity significantly ($P < 0.05$) lower than that with IP.
[b]Incidence of grade 3 or 4 toxicity significantly ($P < 0.05$) higher than that with IP.
[c]Incidence of grade 2 or worse toxicity is significantly ($P < 0.05$) lower than that with IP.
[d]Incidence of grade 2 or worse toxicity significantly ($P < 0.05$) higher than that with IP.
GP, cisplatin plus gemcitabine; IP, cisplatin plus irinotecan; NP, cisplatin plus vinorelbine; TC, carboplatin plus paclitaxel.
AST, aspartate aminotransferase; –, no category in the criteria.

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

quality of life

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

discussion

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

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

Table 4. Second-line treatment

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

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

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

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

appendix

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

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

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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.

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 (stratum 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/m^2 on days 1 and 8 plus cisplatin 80 mg/m^2 on day 1 every 3 weeks, vinorelbine 20–25 mg/m^2 plus gemcitabine 1000 mg/m^2 on days 1 and 8 every 3 weeks, or vinorelbine 20–25 mg/m^2 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 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 2 Treatment delivery

	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)

Table 1 Baseline patients characteristics

Characteristic	6 min drip infusion (n = 41)		1 min bolus injection (n = 42)		P
	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.

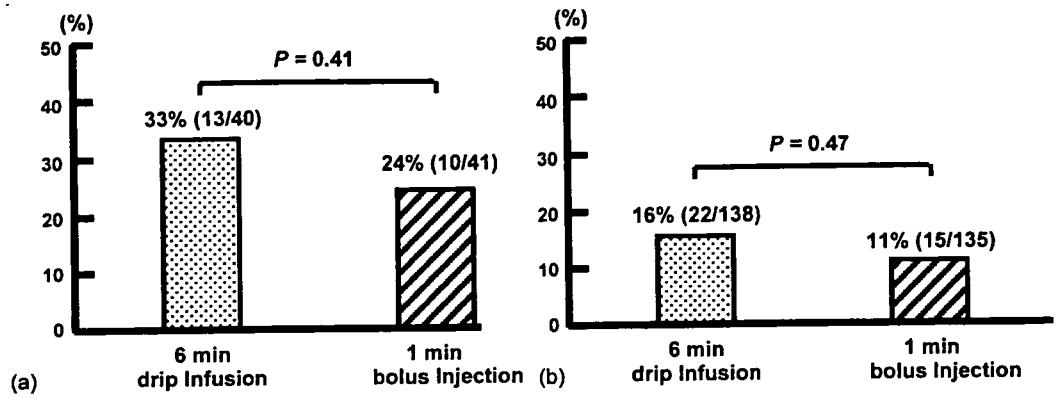

Fig. 1 The incidence of local venous toxicity: (a) per patient, (b) per infusions.

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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Susceptibility to Lung Cancer and Genetic Polymorphisms in the Alcohol Metabolite-related Enzymes Alcohol Dehydrogenase 3, Aldehyde Dehydrogenase 2, and Cytochrome P450 2E1 in the Japanese Population

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BACKGROUND. It is believed that acetaldehyde plays an important role in alcohol-related carcinogenesis; although current epidemiologic studies have provided inconsistent findings on the association between alcohol consumption and the risk of lung cancer.

METHODS. To clarify the hypothesis that genetic polymorphisms in alcohol-metabolizing enzymes may influence susceptibility to lung cancer, the authors conducted a hospital-based case-control study and examined genetic polymorphisms in the alcohol dehydrogenase 3, aldehyde dehydrogenase 2 ($ALDH_2$), and cytochrome P450 2E1 genes in 505 patients with histologically confirmed lung cancer and in a group of 256 noncancer controls who provided complete cigarette and alcohol consumption histories. Genotyping was conducted by polymerase chain reaction-restriction fragment-length polymorphism assay.

RESULTS. A significant association was noted between alcohol consumption and lung cancer risk. Thus, using the median value for the controls as the cut-off point, the odds ratios (OR) for light and heavy drinkers were 1.76 and 1.95, respectively (P for trend = .012), compared with nondrinkers. In addition, there was a significant trend toward increased risk of lung cancer in drinkers with $ALDH_2$ variant alleles (P for trend <.0001). The adjusted OR for heavy drinkers was 6.15 compared with nondrinkers. Regarding associations between histologic type and genotypes, the $ALDH_2$ variant allele was significantly less common in patients who had adenocarcinoma compared with controls.

CONCLUSIONS. The current observations suggested a positive association between alcohol consumption and the risk of lung cancer. Drinking may increase the risk, especially among individuals who have the variant $ALDH_2$ alleles. *Cancer* 2007;110:353–62. *2007 American Cancer Society.*

KEYWORDS: lung cancer, alcohol consumption, case-control study, genetic polymorphism, alcohol dehydrogenase 3, aldehyde dehydrogenase 2, cytochrome P450 2E1.

Epidemiologic studies have provided inconsistent results regarding the associations between alcohol consumption and the risk of lung cancer. In general, therefore, the involvement of alcohol in lung cancer etiology has been regarded with skepticism, with any indication of an association being attributed in most instances to confounding factors, such as cigarette smoking.[1] It indeed is difficult to separate the effects of alcohol and smoking because, the 2 tend to be

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correlated, but this problem does not automatically exclude the possibility that there is a separate alcohol effect. A panel of experts commissioned by the World Cancer Research Fund and the American Institute for Cancer Research in 1997, after reviewing the epidemiologic evidence, concluded that alcohol intake *possibly* may increase lung cancer risk.[2] Although the mechanism by which alcohol may cause cancer remains obscure, many epidemiologic studies have identified chronic alcohol consumption as a significant risk factor for cancers of the oral cavity, pharynx, larynx, and esophagus in humans.[3] When investigating the role of alcohol-related carcinogenesis, most studies have concentrated on the type of alcoholic beverage consumed and the amount of daily intake, but this does not fully explain the variance in individual susceptibility to alcohol-related cancer.

Recent reports strongly implicate acetaldehyde, the first metabolite of ethanol, rather than alcohol itself, as responsible for the risk of developing alcohol-related cancers. It has been reported that acetaldehyde causes mutations by DNA adduct formation and inhibition of DNA repair. Moreover, drinking or inhaling acetaldehyde has mutagenic and carcinogenic effects and induced nasal and laryngeal carcinomas in experimental animals.[4–8]

Ethanol is primarily (80%) oxidized to acetaldehyde by alcohol dehydrogenase (*ADH*), and most of this acetaldehyde is then eliminated by aldehyde dehydrogenase (*ALDH*). However, ethanol and acetaldehyde also are metabolized through the microsomal ethanol-oxidizing system and the microsomal acetaldehyde-oxidizing system, and cytochrome P450 2E1 (*CYP2E1*) is a major contributor to those systems.[9,10] *CYP2E1* has high oxidation activity and is induced by long-term alcohol intake. These enzymes exhibit wide interindividual variability in their activity, suggesting that the variation may be caused by genetic polymorphisms.

There are several *ADH* subtypes, some of which have genetic variants with altered kinetic properties. ADH_3 is polymorphic, and the enzyme encoded by the ADH_3^1 allele metabolizes ethanol to acetaldehyde 2.5 times faster than that encoded by the ADH_3^2 allele.[11] $ALDH_2$ is a key enzyme in the elimination of acetaldehyde. In individuals with $ALDH_2^2$, a variant allele that is prevalent among East Asians (eg, 50% prevalence in Japan[12]), the activity of this enzyme is extremely low. The *CYP2E1* variant allele, which is detectable by *Rsa*I digestion (termed the c2 variant), corresponds to higher activity ethanol metabolism and is associated with greater alcohol consumption.[13–15] Individuals who have 1 or more ADH_3^1, $ALDH_2^2$, and *CYP2E1* c2 alleles accumulate more acetaldehyde in the blood after drinking ethanol and may be at increased risk for various alcohol-related diseases at similar levels of alcohol intake as individuals who do not carry these alleles. Because the ADH_3 variant allele is common in whites, and the $ALDH_2$ and *CYP2E1* variant alleles are found at high frequency in Asians, research on these genes is most advanced regarding alcohol-related diseases and alcohol metabolism.

The association between genetic polymorphisms in these enzymes and susceptibility to some types of cancer has been reported in case-control studies. The ADH_3^1 and $ALDH_2^2$ alleles are associated closely with alcohol-related cancers in the upper aerodigestive tract,[16–21] and systemic acetaldehydemia has been considered responsible for carcinogenesis in this locality. However, to our knowledge, there are no reports on associations between polymorphisms of *ALDH* and lung cancer risk. In relation to *ADH*, a negative association between genetic variation in ADH_3 and lung cancer has been reported recently.[22] *CYP2E1* is responsible primarily for the bioactivation of many low-molecular-weight, tobacco-specific carcinogens, including certain nitrosamines, such as *N*-nitrosodimethylamine and *N*-nitrosonornicotine. It is possible that the *CYP2E1* c2 variant not only may increase the blood concentration of acetaldehyde but also may activate these carcinogens more strongly. Activated nitrosamines have been linked to the development of numerous cancers. However, results from studies that evaluated the role of *CYP2E1* polymorphisms in relation to lung cancer have been discrepant.[23–28] Because previous investigations did not adjust for alcohol consumption and/or did not have sufficient power to distinguish the risk from alcohol consumption, these inconsistent findings may have been caused by variations in *CYP2E1* enzyme activity induced by ethanol.

We conducted a hospital-based case-control study to evaluate whether ADH_3, $ALDH_2$, or *CYP2E1* polymorphisms are associated with lung carcinogenesis. The primary endpoint of the current study was to clarify the association between each genetic polymorphism and the risk of lung cancer, controlling for the amount of alcohol consumed and smoking habits. Furthermore, associations between alcohol consumption and lung cancer risk in individuals with variant alleles, again controlling for smoking, and associations between these polymorphisms and histologic characteristics were evaluated.

MATERIALS AND METHODS

Participants

This study was approved by the Institutional Review Board and the Ethics Committee of the National

Cancer Center, Japan. The majority of eligible participants in this study were residents of Chiba and East Tokyo, and all were of Japanese nationality. Personal and clinical data from patients who participated in the Lung Cancer Database Project at the National Cancer Center Hospital East (NCCH-E) and the National Cancer Center Research Institute East were used in the current study. The database includes information on demographic factors, physical symptoms, psychological factors, and lifestyle factors (diet, smoking, etc) obtained from self-reported questionnaires and medical information from the patients' medical charts and blood, DNA, and urine specimens. All patients who were enrolled in the current study had primary lung cancer that was newly diagnosed with histologic or cytologic confirmation at the Thoracic Oncology Division of the NCCH-E, Japan, from September 1997 to June 2000. All patients provided their written informed consent prior to enrolment in this project. Unmatched controls were newly recruited individuals from the population with no history of cancer or other tumors who visited the Thoracic Oncology Division of NCCH-E from March 2002 to May 2003 and were confirmed as cancer-free by appropriate examinations (chest computed tomography scans, bronchofibroscopy, video-assisted thoracoscopic biopsy, etc). The major reasons for visiting the hospital were suspicions of lung cancer on chest x-ray or sputum cytology at their annual medical check-up or referral from other hospitals. Epidemiologic data were collected by personal interview. All individuals in the control group completed the same standardized questionnaire that was completed by the Lung Cancer Database Project participants, including detailed demographic information, history of cancer, occupational and residential history, and detailed information regarding alcohol and tobacco consumption. All participants provided their written consent.

Sample Collection and DNA Extraction

Four milliliters of peripheral venous blood were collected into heparinized tubes. Genomic DNA was purified from peripheral blood lymphocytes using a DNA isolation kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions and was stored at 80°C.

Polymorphism Analysis

ADH_3 and $ALDH_2$ genotyping was performed by using the polymerase chain reaction-restriction fragment-length polymorphism (PCR-RFLP) method. To prevent the amplification of closely related ADH_1 and ADH_2 genes, samples initially were digested with the *Nla*III restriction enzyme (TOYOBO, Osaka, Japan). A 145-base pair (bp) section of the ADH_3 gene was amplified by PCR using 200 ng of predigested genomic DNA with primers (sense, 5′-GCTTTAAGAGT AAATATTCTGTCCCC-3′; antisense, 5′-AATCTACCTCT zTTCCGAAGC-3′). The PCR product obtained in this manner then was digested directly with restriction enzyme *Ssp*I (TOYOBO). After polyacrylamide gel electrophoresis, ADH_3 alleles were visualized by ethidium bromide and were photographed under ultraviolet light. The ADH_3^1 allele produced fragments of 67 bp, 63 bp, and 15 bp; and the ADH_3^2 allele produced fragments of 131 bp and 15 bp.

A 134-bp fragment of the $ALDH_2$ gene was amplified by PCR according to a slightly modified method of Harada et al.[12] One hundred fifty nanograms of genomic DNA were mixed with 5 pmol of each primer (sense, 5′-CAAATTACAGGGTCAAGGGCT-3′; antisense: 5′-CCACACTCACAGTTTTCTCTT-3′) in a total volume of 50 μL that contained 50 μM deoxynucleotide triphosphate, 1.5 mM $MgCl_2$, and 1 U Taq DNA polymerase; Takara Shuzo, Kyoto, Japan). Thirty-five cycles (denaturation at 94°C for 15 seconds, annealing at 58°C for 1 minute and 30 seconds, and polymerization at 72°C for 30 seconds) were performed using a GeneAmp PCR system 9600 (PerkinElmer, Oak Book, Ill). After purification, each PCR product was digested with *Mbo*II (TOYOBO), electrophoresed on a 20% polyacrylamide gel, stained with ethidium bromide, and photographed. The $ALDH_2^1$ allele produced fragments of 125 bp and 9 bp, and the $ALDH_2^2$ allele produced fragments of 134 bp.

The *CYP2E1* genotypes ascribed to the *Rsa*I site in the 5′-flanking region also were identified as RFLPs by PCR. Genomic DNA (100 ng) was subjected to PCR with each primer (sense, 5′-ATCCACAAGTG ATTTGGCTG-3′; antisense, 5′-CTTCATACAGACCCTC TTCC-3′). PCR was performed for 35 cycles under the following conditions: 1 minute at 95°C for denaturation, 1 minute at 55°C for primer annealing, and 1 minute at 72°C for primer extension. The 412-bp fragment was digested with *Rsa*I (TOYOBO). The products that were yielded were fragments with 360 bp and 50 bp for c1/c1; 360 bp, 50 bp, and 410 bp for c1/c2; and 410 bp for c2/c2 detected by electrophoretic analysis in 5% polyacrylamide gels.

Statistical Analysis

Patient characteristic (see Table 1) were compared with characteristic in the control group by using the Student *t* test or the chi-square test. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were obtained by unconditional logistic regression analy-

TABLE 1
Baseline Characteristics of Lung Cancer Cases and Controls

Characteristic	No. (%) Cases (n = 505)	Controls (n = 256)	*P* for difference
Mean age SD, y	64.8 8.3	63.5 10.2	.06*
Sex			
Men	360 (71.3)	126 (49.2)	
Women	145 (28.7)	130 (50.8)	<.0001†
Smoking status			
Never	140 (27.7)	129 (50.4)	
Past	97 (19.2)	64 (25)	
Current	268 (53.1)	63 (24.6)	<.0001†
Smoking amounts, pack-years			
Past			
<27	35 (36.1)	32 (50)	
27	62 (63.9)	32 (50)	.08†
Current			
<40	71 (26.5)	30 (47.6)	
40	197 (73.5)	33 (52.4)	.001†
Alcohol drinking habit, times/wk			
Seldom	116 (23)	118 (46.1)	
2	43 (8.5)	42 (16.4)	
3–6	96 (19)	22 (8.6)	
Daily	250 (49.5)	74 (28.9)	.0001†
Alcohol amounts, g/day			
0	120 (23.8)	119 (46.5)	
<31.6	154 (30.5)	65 (25.4)	
31.6	231 (45.7)	72 (28.1)	.0001†

SD indicates standard deviation.
* Determined using the Student *t* test.
† Determined using the chi-square test.

sis. In our regression models, we adjusted ORs for potential confounding variables, including age, sex, smoking status (never, past, current) or amounts smoked (pack-years) and alcohol consumed (none, light, heavy). Because differences in the amount of alcohol consumed (ethanol, in gram per day) were very large, we divided those who drank into 3 categories: nondrinkers, light drinkers (31.6 g per day), and heavy drinkers (>31.6 g per day). The amount of tobacco smoke exposure was calculated as pack-years (usual amount per day/20 × overall duration [years] of use). Participants were considered current smokers if they smoked up to 1 year before the date of diagnosis in the case group or up to the date of the interview for the control group. The average amount of daily ethanol intake was calculated in grams. Calculation of this value was based on an average ethanol content of 4-volume% in beer, 15-volume% in Japanese sake (rice wine), 25-volume% in Japanese spirits (syochu), 12-volume% in wine, and 40-volume% in spirits. Drinking frequency was assessed as 5 categories: less than once a week, 1 or 2 days a week, 3 or 4 days a week, 5 or 6 days a week, and daily. Categorical variables were compared with the chi-square test. ORs and 95% CIs were calculated by using logistic regression analysis adjusting for age, sex, smoking, and drinking. The Mantel extension test was used to evaluate linear trends across categories of alcohol consumption that were divided into 4 categories by quartiles for control. Resulting *P* values <.05 (2-tailed) were considered statistically significant. All statistical analyses were performed using the SAS statistical software package (SAS Institute Inc., Cary, NC).

RESULTS

In total 510 patients with lung cancer (cases) and 260 healthy controls participated in this study. Because of the lack of DNA samples or information on lifestyle, 9 participants were eliminated. Table 1 summarizes the baseline characteristics of selected variables for the lung cancer cases and controls. Age distribution was similar in both groups (mean, 64.8 years and 63.5 years, respectively); however, the cases were more likely than the controls to be men (71.3% and 49.2%), to be current smokers (53.1% and 24.6%) and heavy smokers, and to consume more alcohol. The proportions of those who consumed >31.6 g per day of ethanol and of daily drinkers were 45.7% and 49.5%, respectively, for cases and 28.1% and 28.9%, respectively, for controls. The median values from the control group for the 2 smoking amount categories were used as the cut-off values. The 3 categories of alcohol consumption were lifetime nondrinker, below the median intake, and above the median intake.

The frequency of *ADH_3*, *$ALDH_2$*, and *CYP2E1* genotypes and ORs among lung cancer cases and controls are presented in Table 2. After adjustment for age, sex, smoking amount, and amount of alcohol consumed, the ORs for individuals with the *ADH_3*, *$ALDH_2$*, and *CYP2E1* variant alleles, compared with individuals who were homozygous for the common allele, were 1.01, 0.73, and 0.93, respectively. Thus, there were no significant differences in the frequencies of any genotypes between cases and controls. The OR for carriers of the *CYP2E1* c2/c2 genotype, compared with the c1/c1 genotype, was 4.66 ($P < .05$). This genotype is not in Hardy-Weinberg equilibrium in the control population, the observed frequency is most likely an underestimate, and the finding of an association with lung cancer is most likely a false-positive result.

Without taking these genotypes into consideration, a direct association between alcohol consumption and lung cancer occurrence can be derived, as

TABLE 2
The Frequency of Alcohol Dehydrogenase 3, Aldehyde Dehydrogenase 2, and Cytochrome P450 2E1 Genotypes and Odds Ratios Among Lung Cancer Cases and Controls

Genotype	No. (%) Cases (n = 505)	No. (%) Controls (n = 256)	OR Crude	OR Adjusted*
ADH_3				
C/C	459 (90.9)	227 (88.7)	1	1
C/V	44 (8.7)	29 (11.3)	0.75 (0.46–1.23)	0.71 (0.40–1.16)
V/V	2 (0.4)	0 (0)	—	—
C/V and V/V	46 (9.1)	29 (11.3)	0.78 (0.48–1.28)	0.74 (0.44–1.24)
$ALDH_2$				
C/C	319 (63.2)	134 (52.3)	1	1
C/V	168 (33.3)	108 (42.2)	0.65 (0.48–0.90)†	0.73 (0.52–1.03)
V/V	18 (3.6)	14 (5.5)	0.54 (0.26–1.12)	0.75 (0.35–1.59)
C/V and V/V	186 (36.8)	122 (47.7)	0.64 (0.47–0.87)†	0.73 (0.53–1.02)
CYP2E1				
C/C	300 (59.4)	147 (57.4)	1	1
C/V	175 (34.7)	106 (41.4)	0.81 (0.59–1.11)	0.83 (0.60–1.15)
V/V	30 (5.9)	3 (1.2)	4.90 (1.47–16.32)†	4.66 (1.36–16.0)†
C/V and V/V	205 (40.6)	109 (42.6)	0.92 (0.68–1.25)	0.93 (0.68–1.29)

OR indicates odds ratios; *ADH_3*, alcohol dehydrogenase 3; C, common allele; V, variant allele; *$ALDH_2$*, aldehyde dehydrogenase 2; *CYP2E1*, cytochrome P450 2E1.
* ORs were adjusted for age, sex, smoking amounts (pack-years), and alcohol amounts (ethanol: mg per day).
† $P < .05$.

shown in Table 3. Drinking was classified as none, light (31.6 g per day) or heavy (>31.6 g per day). When adjusted for age, sex, and smoking amounts, drinking imposed a significantly greater risk of lung cancer occurrence. The ORs for the light drinkers and heavy drinkers, compared with nondrinkers, were 1.76 and 1.95, respectively (P for trend = .012). Thus, the risk of lung cancer increases as the amount alcohol consumed increases.

ORs for developing lung cancer in association with the *ADH_3*, *$ALDH_2$*, and *CYP2E1* genotypes also are presented in Table 3. Similar to what was observed in all participants taken together, an increased risk for developing lung cancer also was observed among individuals who were homozygous for the common allele ADH_3^{1-1}. However, because there were too few *ADH_3* variant allele carriers to analyze any association between alcohol consumption and lung cancer risk for this allele, it was inappropriate to compare the ADH_3^2 and ADH_3^{1-1} genotypes.

The adjusted OR for the $ALDH_2^{1-1}$ group was 0.75 (95% CI, 0.39–1.42) in light drinkers and 0.46 (95% CI, 0.20–0.99) in heavy drinkers. In contrast, individuals with the $ALDH_2^2$ allele had a significantly greater risk of lung cancer; light drinkers had a 3.6-fold increased risk, and heavy drinkers had a 6.2-fold increased risk compared with nondrinkers (P for trend < .0001). These results indicate that, in individuals with the *$ALDH_2$* variant allele, continuous alcohol consumption is a strong risk factor for lung cancer.

The OR for the *CYP2E1* c1/c1 genotype was 1.81 (95% CI, 0.97–3.38) for light drinkers and 1.67 (95% CI, 0.86–3.21) for heavy drinkers. For individuals with the *CYP2E1* c2 allele, the OR was 1.74 (95% CI, 0.91–3.35) for light drinkers and 2.56 (95% CI, 1.16–5.65) for heavy drinkers (P for trend = .005). These results may indicate that individuals with the *CYP2E1* variant allele are in a high-risk group for lung cancer in heavy drinkers.

It must be emphasized that, because of differences in distribution according to sex between cases and controls, we analyzed relative risks only in men (Table 4). For baseline characteristics among men, higher consumption of alcohol and more smoking were observed, as expected. Regarding associations between alcohol consumption and lung cancer risk, drinking was associated with an increased risk of developing lung cancer in all participants. The adjusted OR for the light and drinkers, compared with nondrinkers, was 6.54 (95% CI, 3.13–13.7) and 6.58 (95% CI, 3.28–13.2), respectively. However, in individuals with active $ALDH_2^{1-1}$ genotypes, there was no association between alcohol consumption and lung cancer risk. In individuals with the inactive $ALDH_2^2$ alleles, the risk for lung cancer was 6.8-fold (95% CI, 2.72–17.1) for light drinkers and 9.3-fold (95% CI, 3.72–23.4) for heavy drinkers compared with nondrinkers (P for trend <.0001). The risk in men who were heavy drinkers was much greater compared with women and those who carried the active $ALDH_2^{1-1}$ genotype.

In individuals with the c2 allele, the risk of lung cancer for light drinkers (OR, 8.31; 95% CI, 2.67–25.9) and for heavy drinkers (OR, 9.93; 95% CI, 3.39–29.1) was increased compared with individuals who were homozygous for the *CYP2E1* c1 allele and compared with the risks in all men. However, it should be noted that, because of the low incidence of homozygosity for variant allele in the control group, statistical power was limited in this instance. Similar assessments also were made in women, but no significant associations between any genotype and lung cancer risk were observed (data not shown).

Table 5 shows the distribution of the *ADH_3*, *$ALDH_2$*, and *CYP2E1* genotypes according to tumor histology. The frequency of the ADH_3^2 allele for all histologic types was similar to the frequency observed in controls. The frequency of the $ALDH_2^2$ allele for squamous cell carcinomas, small cell carci-

TABLE 3
Odds Ratios of Developing Lung Cancer for Alcohol Dehydrogenase 3, Aldehyde Dehydrogenase 2, and Cytochrome P450 2E1 Genotypes Stratified by Drinking Amounts

			Drinkers					
	Nondrinkers		31.6 g/Day			>31.6 g/Day		
Genotype	No.*	Reference	No.*	OR (95% CI)†	P	No.*	OR (95% CI)†	P	P for trend‡
All	120/119	1	154/65	1.76 (1.12–2.75)	.014	231/72	1.95 (1.19–3.21)	.0085	.012
ADH_3									
C/C	112/105	1	141/60	1.59 (0.99–2.55)	.054	206/62	1.88 (1.10–3.21)	.02	.025
C/V and V/V	8/14	1	13/5	4.31 (0.912–20.38)	.065	25/10	3.28 (0.742–14.55)	.12	.17
$ALDH_2$									
C/C	57/41	1	99/39	0.75 (0.39–1.42)	.37	163/54	0.46 (0.2– 0.99)	.049	.03
C/V and V/V	63/78	1	55/26	3.63 (1.76–7.46)	.0005	68/18	6.15 (2.77–13.65)	<.0001	<.0001
CYP2E1									
C/C	72/61	1	95/36	1.81 (0.97–3.38)	.061	133/50	1.67 (0.86–3.21)	.13	.31
C/V and V/V	48/58	1	59/29	1.74 (0.91–3.35)	.097	98/22	2.56 (1.16–5.65)	.02	.005

OR indicates odds ratio; 95% CI, 95% confidence interval; *ADH_3*, alcohol dehydrogenase 3; C, common allele; V, variant allele; *$ALDH_2$*, aldehyde dehydrogenase 2; *CYP2E1*, cytochrome P450 2E1.
* The number of cases/number of controls.
† ORs were adjusted for age, sex, and smoking amount (pack-years).
‡ The Mantel extension test.

TABLE 4
Odds Ratios of Developing Lung Cancer for Alcohol Dehydrogenase 3, Aldehyde Dehydrogenase 2, and Cytochrome P450 2E1 Genotypes Stratified by Drinking Amounts Among Men

			Drinkers					
	Nondrinkers		31.6 g/Day			>31.6 g/Day		
Genotype	No.*	Reference	No.*	OR (95% CI)†	P	No.*	OR (95% CI)†	P	P for Trend‡
All	17/31	1	120/36	6.54 (3.13–13.65)	<.0001	223/59	6.58 (3.28–13.22)	.0001	<.0001
ADH_3									
C/C	15/27	1	110/34	6.14 (2.83–13.29)	<.0001	201/49	7.27 (3.44–15.36)	.0001	<.0001
C/V and V/V	2/4	1	10/2	23.31(1.41–286.0)	.028	22/10	5.43 (0.63–47.09)	.12	.47
$ALDH_2$									
C/C	5/2	1	72/16	1.47 (0.25–8.67)	.67	158/42	1.10 (0.20–6.23)	.91	.29
C/V and V/V	12/29	1	48/20	6.82 (2.72–17.13)	<.0001	65/17	9.33 (3.72–23.39)	.0001	<.0001
CYP2E1									
C/C	10/14	1	77/24	5.22 (1.95–13.94)	.0003	125/42	4.71 (1.85–12.05)	.0012	.08
C/V and V/V	7/17	1	43/12	8.31 (2.67–25.89)	.0001	98/17	9.93 (3.39–29.09)	.0001	<.0001

OR indicates odds ratio; 95% CI, 95% confidence interval; *ADH_3*, alcohol dehydrogenase 3; C, common allele; V, variant allele; *$ALDH_2$*, aldehyde dehydrogenase 2; *CYP2E1*, cytochrome P450 2E1.
* Values shown represent the number of cases/number of controls.
† OR were adjusted for age, sex, and smoking history (pack-years).
‡ Mantel extension test.

nomas, and other histologic types was similar to that observed in controls. However, the *$ALDH_2^2$* allele was significantly less common in patients with adenocarcinomas than in controls (36.1% vs 47.7%; $P = .018$). In contrast, the *CYP2E1* c2/c2 genotype was more common in patients with adenocarcinomas (5.8%) and small cell carcinomas (9.8%) than in controls (1.2%).

In this study, we observed that alcohol consumption was an independent risk factor for lung cancer after adjusting for the influence of smoking (P for trend = .012). Although we assumed that individuals who had the *ADH_3^{1-1}* genotype were at greater risk for lung cancer compared with individuals who had the *ADH_3^2* allele, there was no evidence of an association between lung cancer and the *ADH_3* genotype

TABLE 5
Distribution of Alcohol Dehydrogenase 3, Aldehyde Dehydrogenase 2, and Cytochrome P450 2E1 Genotype According to Histologic Findings

	No. (%)				
		Histologic type			
Genotype	Control group (n = 256)	Adenocarcinoma (n = 330)	Squamous cell (n = 100)	Small cell (n = 51)	Other (n = 24)
ADH_3					
C/C	227 (88.3)	297 (90)	91 (91)	48 (94.1)	23 (95.8)
C/V	29 (11.7)	31 (9.4)	9 (9)	3 (5.9)	1 (4.2)
V/V	0 (0)	2 (0.6)	0 (0)	0 (0)	0 (0)
P for difference*		.35	.52	.25	.28
$ALDH_2$					
C/C	134 (52.3)	211 (63.9)	54 (54)	36 (70.6)	18 (75)
C/V	108 (42.2)	104 (31.5)	45 (45)	13 (25.5)	6 (25)
V/V	14 (5.5)	15 (4.6)	1 (1)	2 (3.9)	0 (0)
P for difference*		.018	.17	.056	.083
CYP2E1					
C/C	147 (57.4)	197 (59.7)	59 (59)	31 (60.8)	13 (54.2)
C/V	106 (41.4)	114 (34.6)	37 (37)	15 (29.4)	9 (37.5)
V/V	3 (1.2)	19 (5.8)	4 (4)	5 (9.8)	2 (8.3)
P for difference*		.0067	.19	.001	.04

ADH_3 indicates alcohol dehydrogenase 3; C, common allele; V, variant allele; *$ALDH_2$*, aldehyde dehydrogenase 2; *CYP2E1*C, cytochrome P450 2E1.
* Chi-square test for comparison with controls.

in any analysis. Because the enzyme activity of $ALDH_2^2$ is extremely low, acetaldehyde accumulates after alcohol intake. We could not demonstrate any association of *$ALDH_2$* genotypes with the risk of lung cancer after adjusting for smoking and the amount of alcohol consumed. However, we observed that individuals who had the $ALDH_2^2$ allele were at a significantly greater risk of lung cancer because of alcohol consumption, although there was a significant trend for lower levels of alcohol consumption in individuals who had the $ALDH_2^{1-1}$ genotype (*P* for trend = .03). We hypothesized that not only the differences in blood acetaldehyde concentrations but also the differences in enzyme activity on tobacco-specific carcinogens contribute to carcinogenesis. However, we produced no evidence that lung cancer risk is related to possession of the *CYP2E1* c2/c2 genotype or that the *CYP2E1* genotype modifies lung cancer susceptibility related to alcohol intake.

DISCUSSION

The control population for this study was recruited from the visitors to the NCCH-E. The majority of patients had false-positive chest x-rays at their annual check-up and had normal chest computed tomography scans, and they were not suffering from any respiratory illness. Furthermore, their family medical histories were similar to those expected in the ordinary Japanese population, although the number of current smokers among both men (42.9%) and women (6.9%) may have been somewhat lower than the average (46.8% and 11.1%, respectively, for 2003 according to the Announcement of the Ministry of Health, Labor, and Welfare). For these reasons, we believe that our control group was not at greater risk of cancer occurrence compared with the regular Japanese population. Moreover, it was not necessary to take into account any biases stemming from the selective inclusion only of consenting participants, because the great majority of both patients and controls agreed to participate in the study.

The data from the control group showed that individuals who had the *$ALDH_2$* wild-type genotype consumed more alcohol than individuals who had the variant genotype. This may suggest that genetic polymorphisms of alcohol-metabolizing enzymes influence drinking habits, because consumption may be limited by the unpleasant reactions caused by the accumulation of acetaldehyde in individuals with *$ALDH_2$* variant genotypes. Nonetheless, habitual drinking can increase consumption because of increased microsomal acetaldehyde-oxidizing system activation, further promoting the oxidation of acetaldehyde. The association between drinking habit and *ADH_3* and *CYP2E1* genotypes remains uncertain.

Regarding correlations between smoking and drinking habits, the coexistence of smoking and