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Impact of smoking on lung cancer risk is stronger in those with the homozygous aldehyde dehydrogenase 2 null allele in a Japanese population

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The main lifestyle contributor to acetaldehyde exposure is the drinking of alcoholic beverages, but tobacco smoke also makes some contribution. Although acetaldehyde is associated with upper aerodigestive tract cancer risk, in accordance with genetically determined acetaldehyde metabolism, it is unclear whether lung cancer, a representative smoking-related cancer, is associated with acetaldehyde or genes impacting its metabolism. We conducted a case–control study to examine possible interaction between smoking and aldehyde dehydrogenase 2 (*ALDH2*) Glu504Lys polymorphism (rs671) on the risk of lung cancer in Japanese. Subjects were 718 lung cancer cases and 1416 non-cancer controls enrolled in the Hospital-based Epidemiologic Research Program at Aichi Cancer Center. Lifestyle factors, including smoking, were determined by self-administered questionnaire. We applied pack-years (PY; categorized into five levels: never, <15, <30, <45 and ≥45) as a marker of cumulative exposure to smoking. The impact of smoking, *ALDH2* genotype, and their interaction on lung cancer risk were assessed by odds ratio (OR) and 95% confidence interval adjusted for potential confounders. Adjusted ORs for PY <15, <30, <45 and ≥45 relative to never smokers among those with Glu/Glu or Glu/Lys were 1.39, 1.80, 3.44 and 6.25, respectively (P-trend = 1.4×10^{-30}). In contrast, ORs among Lys/Lys were 1.01, 10.2, 11.4 and 23.2, respectively (P-trend = 2.6×10^{-7}). Interaction between *ALDH2* genotype (Glu/Glu + Glu/Lys versus Lys/Lys) and cumulative smoking dose was statistically significant ($P = 0.036$) and was consistently observed in the analysis among never-drinkers (interaction $P = 0.041$). These results suggest that *ALDH2* Lys/Lys, a null enzyme activity genotype, modifies the impact of smoking on the risk of lung cancer.

Introduction

Alcohol consumption is an established risk factor for cancers of the head and neck, esophagus, colon and breast (1), an effect for which several biological mechanisms have been proposed (2,3). Interestingly, several recent reviews of epidemiologic studies have suggested a potential role for alcohol in carcinogenesis in the lung (4–6). Acetaldehyde, the first oxidative metabolite of ethanol, strongly impacts upper aerodigestive tract cancer via multiple mutagenic effects on DNA, suggesting that it may also play a role in carcinogenesis in the lung (7,8).

Acetaldehyde, which is also an ingredient in tobacco smoke (9–11), is oxidized into acetate by the aldehyde dehydrogenase (ALDH) enzymes. This oxidation is largely dependent on ALDH2 enzyme. The presence of a functional polymorphic site in *ALDH2* is known, namely 504Glu (*1: active)/504Lys (*2: null) (rs671: G>A). The *ALDH2* 504Lys allele is an inactive subunit, and thus, enzyme activity in individuals with the *ALDH2* Lys/Lys genotype is markedly limited compared with that of those homozygous for *ALDH2* 504Glu. Given that the *ALDH2* 504Lys alleles are clustered in East Asian populations, including Japanese, and their well-established impact on alcohol drinking behavior (12), we speculated that this polymorphism may affect lung cancer risk in Japanese in combination with drinking or smoking behavior. We were particularly interested in the possible interaction between this polymorphism and smoking-related acetaldehyde exposure.

Here, we evaluated the association between the *ALDH2* Glu504Lys polymorphism and the lung cancer risk in a case–control study in a Japanese population.

Materials and methods

Study population

The present subjects were aged 20–79 years and were enrolled between January 2001 and November 2005 in the framework of the second version of the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). Details of the study design and subject characteristics have been described elsewhere (13,14). In brief, the second version of HERPACC was initiated at Aichi Cancer Center Hospital, Nagoya, Japan, in 2001. Information on lifestyle factors as well as a 7 ml blood sample was requested from all first-visit outpatients at our hospital, including cancer and non-cancer patients. Before first examination at our hospital, patients were asked about their lifestyle when healthy or before the current symptoms developed. Responses were systematically collected and checked by trained interviewers. Completed responses were obtained from 96.7% of 29 538 eligible subjects, of whom 50.7% donated a blood sample. Questionnaire data were loaded into the HERPACC database and periodically linked with the hospital cancer registry system to update cancer incidence. All participants gave written informed consent and the study was approved by the Ethics Committee of Aichi Cancer Center.

Cases and controls

Cases were 718 patients (423 adenocarcinomas, 127 squamous cell carcinomas, 66 small cell carcinomas, 49 large cell carcinomas, 14 others and 2 unknown) histologically diagnosed with lung cancer between January 2001 and 2005 at Aichi Cancer Center Hospital with no prior history of any cancer. Control subjects were randomly selected from first-visit outpatients who visited our hospital during the same period. A total of 7054 individuals who completed the questionnaire and provided blood samples and were confirmed not to have cancer according to the cancer registry, medical record and self-report were deemed potential controls. Eventually, 1416 controls were frequency matched with case, age and sex. In previous studies, we assessed the clinical diagnosis among non-cancer outpatients and confirmed that there were almost no abnormal findings or non-specific diseases among them (15). We also confirmed the feasibility of using non-cancer outpatients at our hospital as controls in epidemiological studies on the basis that their general lifestyles were accordant with those of a general population randomly selected from the electoral roll in Nagoya City, Aichi Prefecture (16).

Genotyping of ALDH2

DNA of each subject was extracted from the buffy coat fraction using BioRobot EZ1 and an EZ1 DNA Blood 350 ml kit (Qiagen, Tokyo, Japan) or DNA Blood mini kit (Qiagen). Genotyping for the *ALDH2* Glu504Lys

Abbreviations: ALDH2, aldehyde dehydrogenase 2; HERPACC, Hospital-based Epidemiologic Research Program at Aichi Cancer Center; OR, odds ratio; PY, pack-years.

Table I. Characteristics of cases and controls

	Cases (n = 718), n (%)	Controls (n = 1416), n (%)	OR (95% CI)	P[a]
Age				
<40	20 (2.8)	40 (2.8)	—	
40–49	54 (7.5)	106 (7.5)	—	
50–59	196 (27.3)	390 (27.5)	—	
60–69	277 (38.6)	544 (38.4)	—	
70–79	171 (23.8)	336 (23.7)	—	1.000
Mean age ± SD	61.3 ± 10.0	61.8 ± 9.9		0.262
Sex				
Male	533 (74.2)	1054 (146.8)	—	
Female	185 (25.8)	362 (50.4)	—	0.920
Cumulative exposure to smoking (PY)				
0	176 (24.5)	575 (40.6)	1 (reference)	
<15	45 (6.3)	162 (11.4)	1.36 (0.91–2.04)	0.131
<30	75 (10.4)	204 (14.4)	2.07 (1.44–2.98)	8.6×10^{-5}
<45	131 (18.2)	205 (14.5)	3.82 (2.72–5.37)	1.36×10^{-14}
≥45	286 (39.8)	258 (18.2)	6.83 (4.98–9.36)	7.6×10^{-33}
Unknown	5 (0.7)	12 (0.8)		
Drinking habit				
Never	278 (38.7)	501 (35.4)	1 (reference)	
Former[b]	26 (3.6)	64 (4.5)	0.73 (0.45–1.19)	0.209
Current				
<5 g/day	60 (8.4)	174 (12.3)	0.63 (0.46–0.88)	0.007
<23 g/day	113 (15.7)	272 (19.2)	0.77 (0.58–1.01)	0.057
<46 g/day	94 (13.1)	192 (13.6)	0.91 (0.67–1.23)	0.528
≥46 g/day	132 (18.4)	191 (13.5)	1.29 (0.97–1.72)	0.080
Unknown	15 (2.1)	22 (1.6)		
Family history of lung cancer				
No	640 (89.1)	1289 (91.0)	1 (reference)	
Yes	78 (10.9)	127 (9.0)	1.23 (0.92–1.66)	0.169

CI, confidence interval.
[a]P-values were by chi-squared test or Mann–Whitney test for age and sex. Those for ORs were by Wald test.
[b]Former smokers and drinkers were defined as subjects who had quit smoking and drinking at least 1 year previously.

polymorphism (rs671) was based on TaqMan Assays (Applied Biosystems, Foster City, CA). In our laboratory, the quality of genotyping is routinely assessed statistically using the Hardy–Weinberg test and by retyping of a random sampling of 5% of subjects.

Assessment of alcohol intake and smoking exposure

Consumption of each type of beverage (Japanese 'sake', beer, 'shochu', whiskey and wine) was determined as the average number of drinks per day, which was then converted into a Japanese sake (rice wine) equivalent. One drink equates to one 'go' (180 ml) of Japanese sake, which contains 23 g of ethanol, equivalent to one large bottle (633 ml) of beer, two shots (57 ml) of whiskey and two and a half glasses of wine (200 ml). One drink of shochu (distilled spirit), which contains 25% ethanol, was rated as 108 ml. Total alcohol consumption was estimated as the summarized amount of pure alcohol consumption (g/day) of Japanese sake, beer, shochu, whiskey and wine among current regular drinkers. Cumulative smoking dose was evaluated as pack-years (PY), the product of the number of packs consumed per day and years of smoking.

Statistical analysis

To assess the strength of association between an *ALDH2* polymorphism and risk of lung cancer, odds ratios (ORs) with 95% confidence intervals were estimated using unconditional logistic models adjusted for potential confounders. Potential confounders considered in multivariate analysis were age, sex, smoking, drinking and family history of lung cancer with mutual adjustment of *ALDH2*. Smoking status was divided into five categories considering cumulative exposure to tobacco: 0, <15, <30, <45 or ≥45 PY. Alcohol exposure was also categorized into six levels: never-drinkers, former drinkers and current drinkers of <5, <23, <46 or ≥ 46 g/day. Differences in categorized demographic variables between cases and controls were tested by the chi-squared test. Mean values for age between cases and controls were compared by Student's t-test. Accordance with the Hardy–Weinberg equilibrium was checked for controls using the chi-squared test, and the exact P-value was used to assess any discrepancies between genotype and allele frequency. A P-value <0.05 was considered statistically significant. All analyses were performed using STATA version 10 (Stata Corp., College Station, TX).

Table II. Genotype distributions of *ALDH2* polymorphisms and their impact on the risk of lung cancer in recessive model

	ALDH2			P-value
	Glu/Glu	Glu/Lys	Lys/Lys	
Overall				
n (case–control)	322/688	326/605	70/123	
Model1[a]	1.00 (reference)		1.31 (0.95–1.81)	0.104
Model2[b]	1.00 (reference)		1.10 (0.77–1.57)	0.611

[a]Model 1 adjusted for age, sex and smoking (PY: 0, <15, <30, <45, ≥45 and unknown).
[b]Model 2 adjusted for model 1 with family history of lung cancer and drinking (never, former, current <5 g/d, current <23 g/d, current <46 g/d, current ≥46 g/d and unknown).

Results

Table I shows the distribution of cases and controls by background characteristics. Age and sex were balanced between cases and controls. Heavy smokers in terms of PY were significantly more prevalent among cases than controls (P < 0.001). ORs increased in dose-dependent manner and each of them showed high statistical significance. Drinking habit showed fluctuated association. Those who drank ≥46 g ethanol/day showed marginally increased risk of lung cancer, whereas those who drank <46 g ethanol per day or former drinker showed inverse association with variable statistical significance. No significant association was observed between positive family history and lung cancer risk.

Table II shows genotype distributions for *ALDH2* and its ORs and 95% confidence intervals for lung cancer risk. The frequencies of

Table III. Adjusted OR[a] and 95% CI for cumulative exposure to smoking according to *ALDH2* genotype

	PY										
	Ca/co	0	Ca/co	<15	Ca/co	<30	Ca/co	<45	Ca/co	≥45	*P*-trend
ALDH2											
Glu/Glu	81/285	1.00 (reference)	23/85	1.31 (0.74–2.32)	31/100	1.78 (1.03–3.08)	64/102	3.89 (2.35–6.46)	110/119	6.72 (4.16–10.8)	1.6×10^{-16}
Glu/Lys	80/226	1.00 (reference)	20/62	1.41 (0.76–2.63)	34/93	1.66 (0.97–2.85)	49/84	2.83 (1.67–4.78)	142/134	5.36 (3.35–8.59)	4.5×10^{-14}
Lys/Lys	15/64	1.00 (reference)	2/15	1.01 (0.18–5.64)	10/11	10.2 (2.42–43.1)	18/19	11.4 (3.09–42.0)	25/14	23.2 (6.23–86.5)	2.6×10^{-7}

Ca/co, cases/controls; CI, confidence interval.
[a]ORs adjusted for age, sex, family history of lung cancer, smoking (PY: 0, <15, <30, <45, ≥45 and unknown) and drinking (never, former, current <5 g/d, current <23 g/d, current <46 g/d, current ≥46 g/d and unknown).

polymorphisms were in accordance with the Hardy–Weinberg equilibrium. On analysis of lung cancer overall, no significant elevation of risk was observed by *ALDH2* genotype in per allele model. As shown in Table II, although the association was rather clear between *ALDH2* polymorphism and lung cancer, it was not statistically significant in model 1 adjusted for smoking and matching factors. Association between *ALDH2* Lys/Lys became far from significant if drinking habit was included in the model, indicating strong confounding by drinking and Lys/Lys genotype. Among controls, 117 of 123 (95.1%) were never-drinkers in those with Lys/Lys, whereas 29.5% were never-drinkers among Glu/Glu or Glu/Lys subjects. In addition, heavier smokers were significantly common in those with *ALDH2* Glu/Glu or Glu/Lys subjects (19.1%) compared with Lys/Lys subjects (11.4%).

Table III shows the effects of cumulative exposure to smoking on lung cancer risk by *ALDH2* genotype as adjusted ORs. For *ALDH2*, adjusted ORs showed a marked difference by genotype. The ORs for Glu/Glu and Glu/Lys showed similar point estimates, at 6.72 and 5.36 for PY ≥ 45 compared with PY = 0, respectively, with statistical significance. Interestingly, individuals with *ALDH2* Lys/Lys showed a significantly greater risk of lung cancer with increased exposure to smoking. The ORs for those with PY ≤ 45 in *ALDH2* Lys/Lys was 23.2 compared with PY = 0 ($P = 2.8 \times 10^{-6}$), indicating possible interaction between cumulative exposure to smoking and the *ALDH2* Lys/Lys genotype. In contrast, we did not see any interaction between alcohol drinking and *ALDH2* genotype (data not shown). We explored effect of *ALDH2* Lys/Lys according to cumulative exposure, duration and intensity as shown in Table IV. It also supports that *ALDH2* Lys/Lys has greater impact in those with heavier exposure.

Table V shows stratified analyses according to histology and drinking status. Based on the results in Tables II, III and IV, we dichotomized the *ALDH2* genotype as Glu/Glu + Glu/Lys and Lys/Lys. Overall, adjusted ORs among those with Glu/Glu or Glu/Lys for PY <15, <30, <45 and ≥45 relative to never smokers were 1.39, 1.80, 3.44 and 6.25, respectively (P-trend = 1.4×10^{-30}), versus 1.01, 10.2, 11.4 and 23.2, respectively, for those with Lys/Lys (P-trend = 2.6×10^{-7}). We observed a statistically significant interaction between *ALDH2* genotype (Glu/Glu + Glu/Lys versus Lys/Lys) and cumulative dose of smoking (interaction $P = 0.036$). By histologic type, significant interaction was observed in adenocarcinoma (interaction $P = 0.009$), but others were not evaluable owing to the limited number of low-exposure subjects. Interestingly, a significant interaction between the *ALDH2* Lys/Lys genotype and cumulative smoking dose was consistently observed in never-drinkers (interaction $P = 0.041$), indicating that the interaction might exist independent of drinking (Table V).

Table IV. Adjusted OR and 95% CI for *ALDH2* Lys/Lys relative to *ALDH2* Glu/Glu and Glu/Lys according to smoking exposure[a]

Cumulative exposure to smoking	Ca/co Glu/Glu + Glu/Lys	Ca/co Lys/Lys	Odds ratio[b]	*P*-value
Cumulative exposure to smoking				
0	161/511	15/64	0.73 (0.40–1.35)	0.316
<15	43/147	2/15	0.41 (0.09–1.91)	0.258
<30	65/193	10/11	3.51 (1.37–8.97)	0.009
<45	113/186	18/19	1.77 (0.87–3.60)	0.113
≥45	261/244	25/14	1.82 (0.91–3.64)	0.09
Years of smoking				
0	161/11	15/64	0.73 (0.40–1.35)	0.316
<20	37/150	3/18	0.77 (0.21–2.84)	0.699
<40	198/381	28/21	2.81 (1.51–5.20)	0.001
≥40	247/242	24/20	1.29 (0.69–2.44)	0.427
Intensity of smoking (pieces per day)				
0	162/511	15/64	0.73 (0.40–1.35)	0.316
<20	99/233	10/18	1.33 (0.58–3.03)	0.498
<40	278/393	38/33	2.06 (1.23–3.45)	0.006
≥40	107/147	7/8	1.02 (0.33–3.14)	0.966

Ca/co, cases/controls; CI, confidence interval.
[a]Subjects who were unknown for cumulative smoking were excluded from analyses.
[b]ORs adjusted for age, sex, family history of lung cancer, smoking (PY: 0, <15, <30, <45, ≥45 and unknown) and drinking (never, former, current <5 g/d, current <23 g/d, current <46 g/d, current ≥ 46 g/d and unknown).

Discussion

In this study, we found a significant gene–environment interaction between cumulative exposure to smoking and *ALDH2* Lys/Lys for the risk of lung cancer among a Japanese population. A significant interaction among never-drinkers only strongly suggests that this interaction was independent of drinking behavior. In contrast, we did not find an association between lung cancer and *ALDH2* polymorphism alone.

Given the strong evidence for gene–environment interaction between alcohol drinking and *ALDH2* polymorphism in aerodigestive tract cancers in Japanese populations (17–19), we were interested to examine the possible role of the functional genetic polymorphisms involved in acetaldehyde metabolism, *ALDH2* Glu504Lys, in lung cancer. To our knowledge, only a few studies have investigated the association between lung cancer and *ALDH2* polymorphism (20,21). Yokoyama *et al.* (20) reported that the *ALDH2* Lys allele was associated with an increased risk of lung cancer among Japanese alcoholics, albeit in a study population of only seven cases. Minegishi *et al.* examined the impact of *ALDH2* in combination with drinking habit in 505 cases and 256 unmatched controls, who were extensively screened as non-cancer by chest computed tomography, bronchofibroscopy and video-assisted thoracoscopic biopsy under suspicion of lung cancer. Results showed a highly significant increase in the risk of lung cancer by alcohol consumption in those with the *ALDH2* Lys allele. When adjusted for age, sex and alcohol consumption, however, risk for individuals with the *ALDH2* Lys allele in these studies was not further increased by smoking. In contrast, we saw no evidence of interaction between *ALDH2* genotype and drinking behavior, which does not support the previous studies. Interaction between alcohol drinking and *ALDH2* polymorphism in the risk of lung cancer therefore remains to be determined.

Table V. Adjusted OR[a] and 95% CI for the impact of smoking, *ALDH2* genotype and their interaction on lung cancer risk according to histrogical subtype and drinking status

	PY										
ALDH2	Ca/co	0	Ca/co	<15	Ca/co	<30	Ca/co	<45	Ca/co	≥45	*P*-interaction
Overall[b]											
Glu/Glu + Glu/Lys	161/511	1.00 (reference)	43/147	1.39 (0.92–1.05)	65/193	1.80 (1.23–2.12)	113/186	3.44 (2.41–4.97)	261/244	6.25 (4.49–8.70)	
Lys/Lys	15/64	1.00 (reference)	2/15	1.01 (0.18–5.64)	10/11	10.2 (2.42–43.1)	18/19	11.4 (3.09–42.0)	25/14	23.2 (6.23–86.5)	0.036
Histology											
Adenocarcinoma											
Glu/Glu + Glu/Lys	143/511	1.00 (reference)	27/147	0.95 (0.58–1.54)	42/193	1.36 (0.88–2.10)	55/186	1.95 (1.28–2.97)	107/244	3.04 (2.08–4.45)	
Lys/Lys	13/64	1.00 (reference)	2/15	1.19 (0.21–6.75)	7/11	7.71 (1.68–35.4)	10/19	7.00 (1.69–26.6)	13/14	13.6 (3.31–55.6)	0.009
Squamous/small cell carcinoma											
Glu/Glu + Glu/Lys	2/511	1.00 (reference)	7/147	14.9 (2.93–75.5)	18/193	27.5 (6.01–126.3)	40/186	63.9 (14.3–285.4)	111/244	129.8 (29.5–571.9)	
Lys/Lys	0/64	1.00 (reference)	0/15	NE	1/11	NE	4/19	NE	9/14	NE	NE
Drinking											
Never											
Glu/Glu + Glu/Lys	98/246	1.00 (reference)	13/17	2.77 (1.22–6.29)	19/39	2.14 (1.07–4.27)	21/31	3.15 (1.53–6.47)	57/47	6.00 (3.23–11.2)	
Lys/Lys	15/61	1.00 (reference)	2/14	0.96 (0.17–5.43)	10/11	9.17 (2.17–38.7)	18/19	10.1 (2.75–37.3)	23/12	22.2 (5.80–84.9)	0.041
Ever											
Glu/Glu + Glu/Lys	63/266	1.00 (reference)	30/130	1.21 (0.73–2.00)	46/154	1.71 (1.07–2.73)	92/155	3.44 (2.24–5.29)	204/197	6.20 (4.16–9.26)	
Lys/Lys	0/3	1.00 (reference)	0/1	NE	0/0	NE	0/0	NE	2/2	NE	NE

Ca/co, cases/controls; CI, confidence interval; NE, not estimated.

[a]Adjusted for age, sex and smoking (PY: 0, <15, <30, <45, ≥45 and unknown), family history of lung cancer and drinking (never, former, current <5 g/d, current <23 g/d, current <46 g/d, current ≥46 g/d and unknown).

[b]Five cases and 12 controls were excluded from analysis because of unknown PY status.

In addition to being a metabolite of alcohol, acetaldehyde is also a constituent of tobacco smoke (10,11,22). Our present results show that the influence of exposure to acetaldehyde in cigarettes on lung cancer risk, which might be surrogated by cumulative smoking exposure, is remarkably stronger in individuals with Lys/Lys, who cannot metabolize acetaldehyde well. The possibility that this finding was confounded by alcohol consumption can be excluded since statistical significance was adequately reflected on the interaction in never-drinkers. The hypothesis that increased acetaldehyde concentrations contribute to the development of lung cancer is possible because the *ALDH2* Lys/Lys genotype almost completely lacks acetaldehyde oxidation activity. Nevertheless, we cannot deny the possible presence of an unknown gene that is both linked to *ALDH2* polymorphism and at the same time relevant to the metabolism and detoxification of carcinogens in tobacco smoke, albeit that no such gene has been reported to date. It is thought that *ALDH2* itself has no power to directly detoxify carcinogenic compounds in tobacco other than acetaldehyde and that detoxification ability in Lys/Lys individuals might be poor. In any case, confirmation of this association and clarification of its background mechanism are essential.

We note that distribution of histology was different between *ALDH2* Lys/Lys and others. Among ever smokers without history of drinking, adenocarcinoma was significantly more prevalent in those with *ALDH2* Lys/Lys (70.5%) compared with other genotypes (51.7%). This may suggest that possible involvement of acetaldehyde from either sources, smoking or drinking, in adenocarcinoma.

Our study had several methodological strengths and weaknesses. One strength is that it was conducted in a single region in central Japan with a substantial number of subjects and a high response rate. Although controls were selected from non-cancer patients at Aichi Cancer Center Hospital, it is reasonable to assume the same base population as that from which the cases were selected, warranting internal validity. In terms of controls, we previously confirmed that questionnaire-based lifestyle characteristics in this population were similar to those of the general population in Nagoya City in terms of a range of exposures of interest in HERPACC-I (16) and HERPACC-II (H. Ito, K. Matsuo, M. Inoue, K. Tajima, unpublished data), warranting the study's external validity. In addition, the equivalence of genotype distribution for the *ALDH2* polymorphism between our controls and those in public databases and former studies (21,23) for Japanese indicates a lack of bias in the selection of controls, justifying the external validity of our observation. A second strength was that potential confounding by age and sex was addressed by matching of these factors in cases and controls, and smoking and drinking were adjusted in the models.

One weakness of our study was that it was unclear whether the cumulative dose of smoking reflected cumulative exposure to acetaldehyde. A second potential weakness was residual confounding by known or unknown risk factors; in particular, the limited number of cases, particularly in stratified analyses by genotype, indicates the need to replicate our findings in a larger study. A third potential weakness was the information bias intrinsic to case–control studies. The HERPACC system is less prone to this bias than typical hospital-based studies, however, as the data for most if not all patients were collected before diagnosis. In particular, subjects and investigators had no information about *ALDH2* genotype, limiting the impact of information bias in the analysis.

In conclusion, our case–control study showed that the *ALDH2* Lys/Lys genotype, which results in null enzyme activity, modified the impact of smoking on the risk of lung cancer in a Japanese population. This result suggests the possible contribution of acetaldehyde to the pathogenesis of lung cancer. Further replication study is warranted.

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ORIGINAL REPORT

Randomized Phase III Trial of Platinum-Doublet Chemotherapy Followed by Gefitinib Compared With Continued Platinum-Doublet Chemotherapy in Japanese Patients With Advanced Non–Small-Cell Lung Cancer: Results of a West Japan Thoracic Oncology Group Trial (WJTOG0203)

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See accompanying editorial on page 713 and article on page 744

ABSTRACT

Purpose
Gefitinib is a small molecule inhibitor of the epidermal growth factor receptor tyrosine kinase. We conducted a phase III trial to evaluate whether gefitinib improves survival as sequential therapy after platinum-doublet chemotherapy in patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Chemotherapy-naïve patients with advanced stage (IIIB/IV) NSCLC, Eastern Cooperative Oncology Group performance status of 0 to 1, and adequate organ function were randomly assigned to either platinum-doublet chemotherapy up to six cycles (arm A) or platinum-doublet chemotherapy for three cycles followed by gefitinib 250 mg orally once daily, until disease progression (arm B). Patients were stratified by disease stage, sex, histology, and chemotherapy regimens. The primary end point was overall survival; secondary end points included progression-free survival, tumor response, safety, and quality of life.

Results
Between March 2003 and May 2005, 604 patients were randomly assigned. There was a statistically significant improvement in progression-free survival in arm B (hazard ratio [HR], 0.68; 95% CI, 0.57 to 0.80; $P < .001$); however, overall survival results did not reach statistical significance (HR, 0.86; 95% CI, 0.72 to 1.03; $P = .11$). In an exploratory subset analysis of overall survival by histologic group, patients in arm B with adenocarcinoma did significantly better than patients in arm A with adenocarcinoma (n = 467; HR, 0.79; 95% CI, 0.65 to 0.98; $P = .03$).

Conclusion
This trial failed to meet the primary end point of OS in patients with NSCLC. The exploratory subset analyses demonstrate a possible survival prolongation for sequential therapy of gefitinib, especially for patients with adenocarcinoma.

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INTRODUCTION

Lung cancer is the most common cancer worldwide, with an estimated 1.2 million new cases globally (12.3% of all cancers) and 1.1 million deaths (17.8% of all cancer deaths) in 2000.[1] The estimated global incidence of non–small-cell lung cancer (NSCLC) in 2000 was approximately 1 million, which accounted for approximately 80% of all cases of lung cancer.[1] Treatment of advanced NSCLC is palliative; the aim is to prolong survival without leading to deterioration in quality of life.[2] The recommended first-line treatment of advanced NSCLC currently involves up to six cycles of platinum-based combination chemotherapy, with no single combination recommended over another.[3,4] Recently, combination chemotherapy of pemetrexed plus cisplatin was significantly superior to gemcitabine plus cisplatin in nonsquamous NSCLC.[5]

Gefitinib is an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that blocks the signal transduction pathways

implicated in the proliferation and survival of cancer cells.[6] In two phase II trials in patients with pretreated advanced NSCLC (Iressa Dose Evaluation in Advanced Lung Cancer [IDEAL] 1 and 2), gefitinib 250 mg/d showed response rates of 12% and 18% and a median survival time (MST) of 7.0 and 7.6 months in IDEAL1 and 2, respectively; in addition, the toxicity profile was not severe.[7,8] This favorable tolerability profile, coupled with a mechanism of action that is distinct from that of cytotoxic agents, provides a strong rationale for use of gefitinib in combination with standard cytotoxic regimens. Platinum-doublet chemotherapy added to gefitinib in untreated patients with NSCLC was evaluated in two large-scale, placebo-controlled, randomized trials (INTACT-1 and -2).[9,10] Gefitinib showed no survival benefit over placebo when combined with standard platinum-doublet chemotherapy in both trials. Furthermore, gefitinib did not improve time to progression or objective tumor response over chemotherapy alone. These results were disappointing and surprising because of the significant antitumor activity of gefitinib when given alone to pretreated patients with NSCLC.

First, it is possible that each of the agents is working against a susceptible subpopulation of tumor cells so that the effect is redundant rather than additive, or that one agent results in the loss of an intermediary molecule that is essential to the function of the other agent, resulting in an antagonistic effect. Second, patients included in these studies were not selected on the basis of a specific biomarker, such as target EGFR expression, gene amplification, or mutations. Clinical profiles of females, never smokers, adenocarcinoma histology, and Asian ethnicity have all been recognized as favorable subgroups that respond to gefitinib.[11-14]

Because no additive effect was observed by administering gefitinib continuously in combination with chemotherapy, possible alternatives could be the administration of gefitinib in the interval between chemotherapy cycles or as sequential treatment after chemotherapy. This could also potentially prevent the problem of drug interference or antagonism. We conducted a randomized phase III trial to evaluate whether gefitinib improves survival as sequential therapy after platinum-doublet chemotherapy in chemotherapy-naive patents with NSCLC.

PATIENTS AND METHODS

Patients

Eligible patients were 20 to 75 years of age, with histologically or cytologically confirmed stage IIIB (with malignant pleural effusion or contralateral hilar lymph node metastases) or stage IV NSCLC who had not previously received any chemotherapy. Patients who had recurrence after complete surgical resection were permitted. Patients treated with either adjuvant or neoadjuvant chemotherapy were excluded in this trial. Additional criteria included a Eastern Cooperative Oncology Group performance status of 0 to 1, and adequate organ function as indicated by WBC count $\geq$ 4,000/μL, absolute neutrophil count $\geq$ 2,000/μL, hemoglobin $\geq$ 9.5 g/dL, platelets $\geq$ 100,000/μL, AST/ALT $\leq$ 2.5 times the upper limit of normal, total bilirubin $\leq$ 1.5 mg/dL, serum creatinine $\leq$ 1.2 mg/dL, and PaO_2 in arterial blood $\geq$ 70 mmHg. Asymptomatic brain metastases were allowed provided that they had been irradiated and were clinically and radiologically stable. Patients were excluded from the study if they had radiologically and clinically apparent interstitial pneumonitis or pulmonary fibrosis. All patients provided written informed consent, and the study protocol was approved by the West Japan Thoracic Oncology Group Protocol Review Committee and the institutional review board of each participating institution.

Treatment Plan

Eligible patients were centrally registered at West Japan Thoracic Oncology Group Data Center and were randomly assigned to receive either platinum-doublet chemotherapy up to six cycles (arm A) or three cycles of platinum doublet followed by gefitinib 250 mg/d orally, until disease progression (arm B). Patients who achieved disease control (response or stable disease) treated with three cycles of platinum-doublet went for gefitinib treatment phase in arm B. Each physician selected his/her chemotherapy options before randomization. Platinum-doublet chemotherapy options included any of the following: (1) carboplatin area under the curve 6, day 1, and paclitaxel 200 mg/m^2, day 1, every 3 weeks; (2) cisplatin 80 mg/m^2, day 1, and irinotecan 60 mg/m^2, days 1, 8, 15, every 4 weeks; (3) cisplatin 80 mg/m^2, day 1, and vinorelbine 25 mg/m^2, days 1, 8, every 3 weeks; (4) cisplatin 80 mg/m^2, day 1, and gemcitabine 1,000 mg/m^2 days 1, 8, every 3 weeks; or (5) cisplatin 80 mg/m^2, day 1, and docetaxel 60 mg/m^2 day 1, every 3 weeks. The dose of carboplatin was calculated using Calvert's formula, and the glomerular filtration rate was estimated by the Cockcroft-Gaut formula. These treatment schedules and doses are used as standard platinum-doublet regimens for advanced NSCLC in Japan.[15,16]

Randomization was stratified according to the institution, type of histology (adenocarcinoma *v* nonadenocarcinoma), clinical stage (IIIB *v* IV), and selected platinum-doublet regimens with the use of a minimization procedure. Patients receiving platinum-doublet chemotherapy received standard supportive treatments, including hydration and antiemetics, according to each institutional standard guideline. After withdrawing from the trial as a result of disease progression or intolerable toxicity, any systemic treatment, including with EGFR-TKI, was permitted in both arms.

Baseline and Follow-Up Assessments

Pretreatment evaluation included a complete medical history and physical examination, a CBC with differential and platelet count, standard biochemical profile, ECG, chest radiographs, computed tomography (CT) scans of the chest, abdomen, and brain, magnetic resonance imaging, and a whole-body bone scan. During treatment, a CBC and biochemical tests were performed at least every 2 weeks. A detailed medical history was taken and a complete physical examination with clinical assessment was performed every 2 weeks to assess disease symptoms and treatment toxicity, and chest

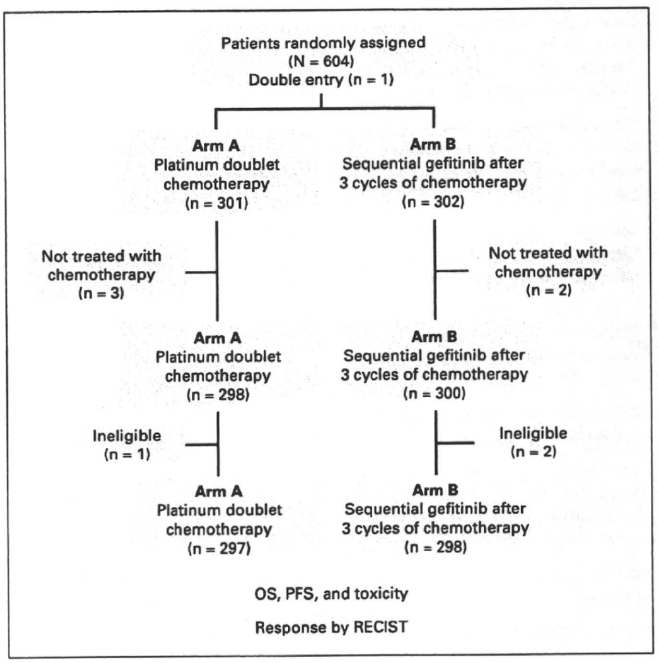

Fig 1. CONSORT diagram for the study. OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

radiographs were done every treatment cycle. Toxicity was evaluated according to the National Cancer Institute Cancer Common Toxicity Criteria (NCI-CTC) version2.[17]

All patients were assessed for response by CT scans monthly during treatment. Response Evaluation Criteria in Solid Tumors (RECIST) were used for the evaluation of response.[18]

Disease-related symptoms were assessed using the Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung quality of life instrument (version 4.0).[19] Patients were asked to complete the instrument at the time of enrollment and at 12 weeks and 18 weeks after initiation of treatment. The maximum attainable score on the LCS was 28, where the patient was considered asymptomatic.

Statistical Analysis

The primary end point was OS; secondary end points included PFS, tumor response, safety, and quality of life. Based on previous trials evaluating platinum-doublet chemotherapy, the MST was approximately a range of 8 to 11 months.[3] In IDEAL-1, which was the trial of gefitinib alone in patients with previously treated NSCLC, median time to treatment failure was 98 days.[7] This trial was designed to detect a 3-month difference in MST. To attain 80% power at a two-sided significance level of .05, assuming a MST in the chemotherapy alone arm of 9 months with 2 years of follow-up after 3 years of accrual, 225 patients in each treatment group were required. Both the OS and PFS were estimated with the Kaplan-Meier method. Comparisons of OS and PFS between arms were assessed by the stratified log-rank test. Two interim analyses were planned after half the patients were registered and at the end of registration.

At the first interim analysis, 14% of patients in arm B unexpectedly withdrew from sequential gefitinib treatment after the three cycles of platinum-doublet chemotherapy at their own request because of hearing the news of interstitial lung disease (ILD) as a result of the use of gefitinib in Japan. If 15% of patients treated with sequential gefitinib withdrew, 284 patients in each arm were required to attain an 80% power at a two-sided significance level of .05, assuming a MST of the chemotherapy alone arm of 9 months with 2 years of follow-up after 3 years of accrual. Consequently, a protocol amendment was performed in April 2004.

For symptom analysis, comparisons of LCS between arms were conducted using a linear mixed-effects model in which the missing data depend on the observed LCS, using the MIXED procedure in SAS version 9 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

From March 2003 to May 2005, 604 patients with advanced NSCLC from 39 institutions were enrolled (Appendix, online only). Patients were randomly assigned to platinum-doublet chemotherapy up to 6 cycles (n = 302, arm A) or sequential gefitinib after three cycles of platinum-doublet chemotherapy (n = 302, arm B). One patient was double entry in arm A, and three patients in arm A and two in arm B did not receive any chemotherapy. Therefore, a total of 598 patients (298 in arm A and 300 in arm B) were included in the analysis of patients' profiles and the assessment for toxicity. In addition, three patients did not meet the entry criteria; thus, 297 patients with measurable lesions by RECIST in arm A and 298 eligible patients in arm B were assessable for OS, PFS, and response. Figure 1 shows the CONSORT diagram. Table 1 presents baseline patient characteristics and lists the platinum-doublet chemotherapy regimen selected by each physician.

Table 1. Patients' Characteristics and Selected Platinum-Doublet Chemotherapy Regimens

Parameter	Arm A		Arm B		
	No. of Patients	%	No. of Patients	%	*P*
Patients enrolled	298		300		—
Median age, years	63		62		.114
Range	35-74		25-74		
Sex					
Male	191	34.6	192	64.0	.981
Female	107	67.8	108	36.0	
ECOG PS					
0	103	30.8	90	30.0	.778
1	195	69.2	210	70.0	
Histology					
Adenocarcinoma	232	77.9	237	79.0	.733
Nonadenocarcinoma	66	22.1	63	21.0	
Clinical stage					
IIIB	54	18.1	55	18.3	.946
IV	244	81.9	245	81.7	
Smoking status					
Smoker	202	67.8	210	70.0	.559
Nonsmoker	96	32.2	90	30.0	
Selected platinum-doublet chemotherapy regimens					
CP	193	64.8	195	65.0	.987
IP	8	2.7	10	3.3	
VP	44	14.8	45	15.0	
GP	45	15.1	42	14.0	
DP	8	2.7	8	2.7	

NOTE. Differences between two arms were tested by χ^2 test, excluding age (Wilcoxon test), ECOG PS.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; CP, carboplatin and paclitaxel; IP, irinotecan and cisplatin; VP, vinorelbine and cisplatin; GP, gemcitabine and cisplatin; DP, docetaxel and cisplatin.

Treatment Delivery

The median number of chemotherapy cycles was three (range, 1 to 6) in arm A, and three (range, 1 to 3) in arm B. One hundred seventy-two patients (57.3%) in arm B were treated with gefitinib after completion of three cycles of platinum-doublet. The median treatment duration of gefitinib was 69.5 days, and the maximum treatment duration was 1,324 days. As presented in Figure 2, EGFR-TKIs, which included gefitinib, erlotinib, and vandetanib, were used in 54.5% and 75.2% of patients in arm A and B, respectively, at any time during treatment of NSCLC. In arm B, gefitinib treatment did not take place because of early disease progression before the completion of three cycles of platinum-doublet chemotherapy in 93 patients (31.2%), and 33 (11.1%) in arm B rejected the use of gefitinib after platinum-doublet because of publication of a news report about gefitinib-induced ILD.

Treatment Efficacy

At the time of final analysis, 247 (83.2%) and 232 patients (78.0%) had died in arm A and arm B, respectively. The MST was 12.9 months for chemotherapy alone and 13.7 months for chemotherapy followed by gefitinib (hazard ratio [HR] according to Cox's regression model, 0.86; 95% CI, 0.72 to 1.03; $P = .11$ stratified log-rank test, Fig 3A). The PFS was 4.3 months in arm A and 4.6 months in arm B (HR, 0.68; 95% CI, 0.57 to 0.80; $P < .001$, Fig 3B).

When exploratory subset analysis were performed, sequential therapy with gefitinib after three cycles of platinum-doublet chemotherapy prolonged OS significantly in the subset of patients with adenocarcinoma (HR, 0.79; 95% CI, 0.65 to 0.98; $P = .03$; Fig 4A). There was no significant difference in OS due to the small subset of patients with nonadenocarcinoma (HR, 1.24; 95% CI, 0.85 to 1.79; $P = .25$; Fig 4B). In addition to the OS plots, the PFS plots for adenocarcinoma and nonadenocarcinoma were showed in Figure 4C and 4D, respectively. Furthermore, results of the subset analysis were summarized for forest plots in Figure 5. Another subset of smokers had a survival advantage with chemotherapy followed by gefitinib over chemotherapy alone. There was no difference between the two treatment groups in the subset of never smokers. Never smokers with NSCLC had a prolonged survival of about 23.5 months in arm A and 21.7 months in arm B.

The overall response rate was 29.3% for chemotherapy alone and 34.2% for chemotherapy followed by gefitinib. There was no significant difference between treatment arms ($P = .20$; Fisher's exact test). The overall disease control rate (response and stable disease) were 71.0% and 75.5% in arm A and in arm B, respectively ($P = .22$).

Toxicity

Toxicity was assessed according to NCI-CTC version 2 in all patients who received at least one treatment cycle of platinum-doublet chemotherapy (Table 2). Grade 3 or 4 anemia developed in 21.8% of patients in arm A and 13.3% of patients in arm B. There was a significant difference between the two arms ($P = .006$). Grade 3 or 4

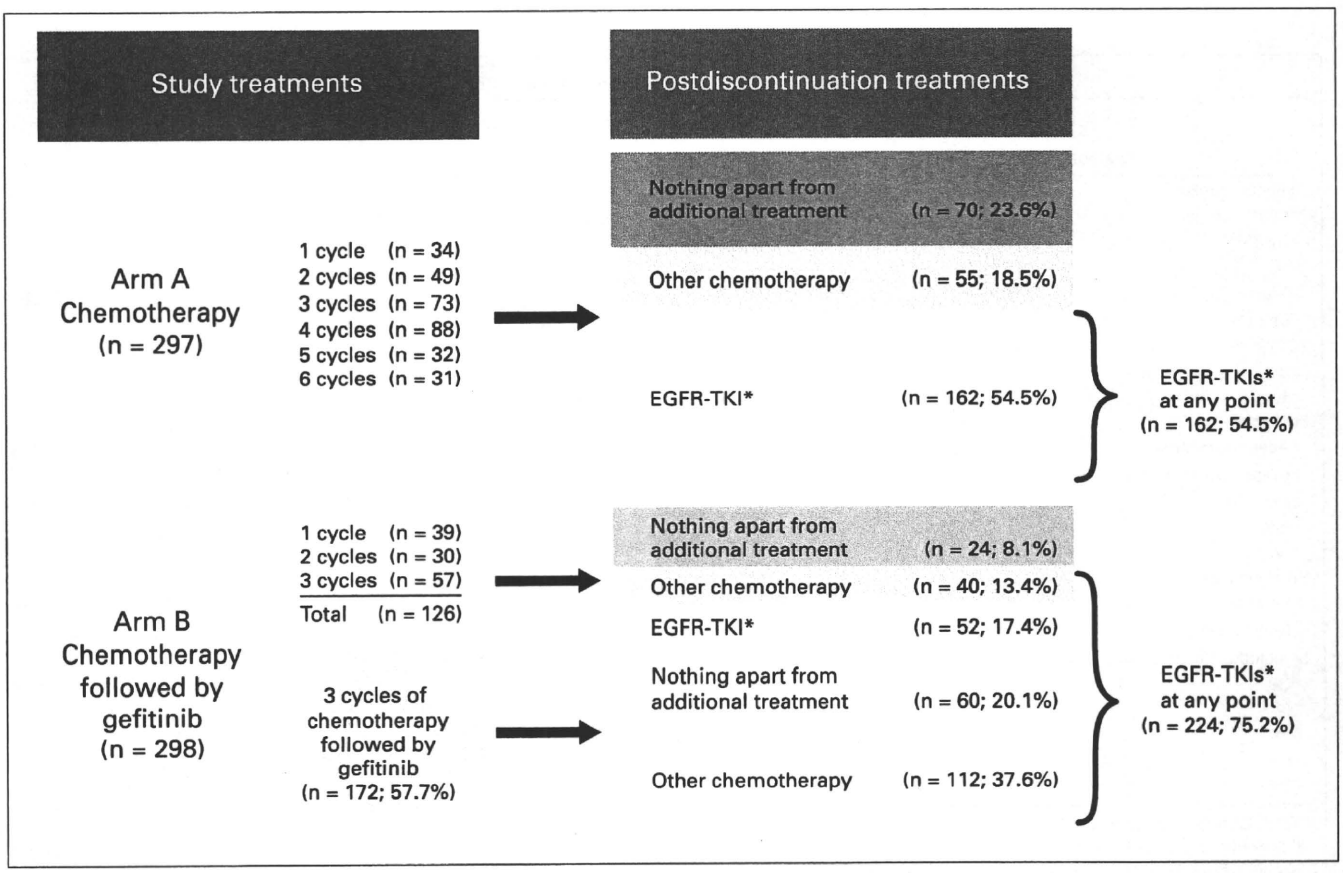

Fig 2. Exposure to active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), including postdiscontinuation treatments in the full analysis set population (n = 595).

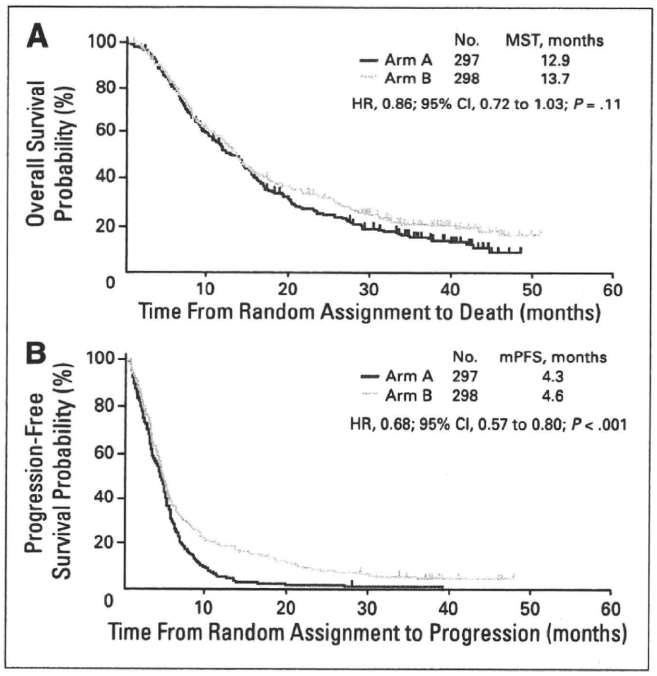

Fig 3. (A) Overall survival and (B) progression-free survival (n = 598). MST, median survival time; HR, hazard ratio; mPFS, median progression-free survival.

thrombocytopenia occurred in 10.7% of patients in arm A and 6.3% of patients in arm B, but differences did not reach significance ($P = .054$). Conversely, grade 3 or 4 AST/ALT elevation in arm B was severer than in arm A ($P = .002$). Severe ILD induced by gefitinib, which many patients feared developing, was observed in two patients in this study.

Disease-Related Symptoms Assessment

All 595 patients completed baseline LCS questionnaires; questionnaire completion rates were 81.0% at 12 weeks and 70.3% at 18 weeks. LCS data were missing in 111 surveys because of death or severe impairment of the patient's general condition; this accounted for 6.2% of the total number of surveys scheduled. The adjusted mean of initial summed scores of LCS were 20.3 for arm A and 20.6 for arm B, respectively. The adjusted LCS scores at 12 and 18 weeks were 21.0 and 20.9 for arm A, and 21.8 and 21.2 for arm B, respectively. Sequential gefitinib seemed to provide better symptom relief, although differences did not reach statistical significance ($P = .10$).

DISCUSSION

Sequential gefitinib therapy after three cycles of standard platinum-doublet chemotherapy showed no survival benefit over platinum-doublet chemotherapy up to six cycles in previously untreated patients with advanced NSCLC. However, sequential gefitinib was associated with significantly prolonged PFS. Recently, positive results with maintenance or sequential chemotherapy have been reported in clinical trials in PFS or time to progression; however, OS was not significantly lengthened.[20,21] More recently, pemetrexed administered to NSCLC patients without progression after four cycles of first-line treatment with platinum-doublet provided significant improvement in PFS compared with placebo (HR, 0.60; 95% CI, 0.49 to 0.73; $P < .00001$).[22]

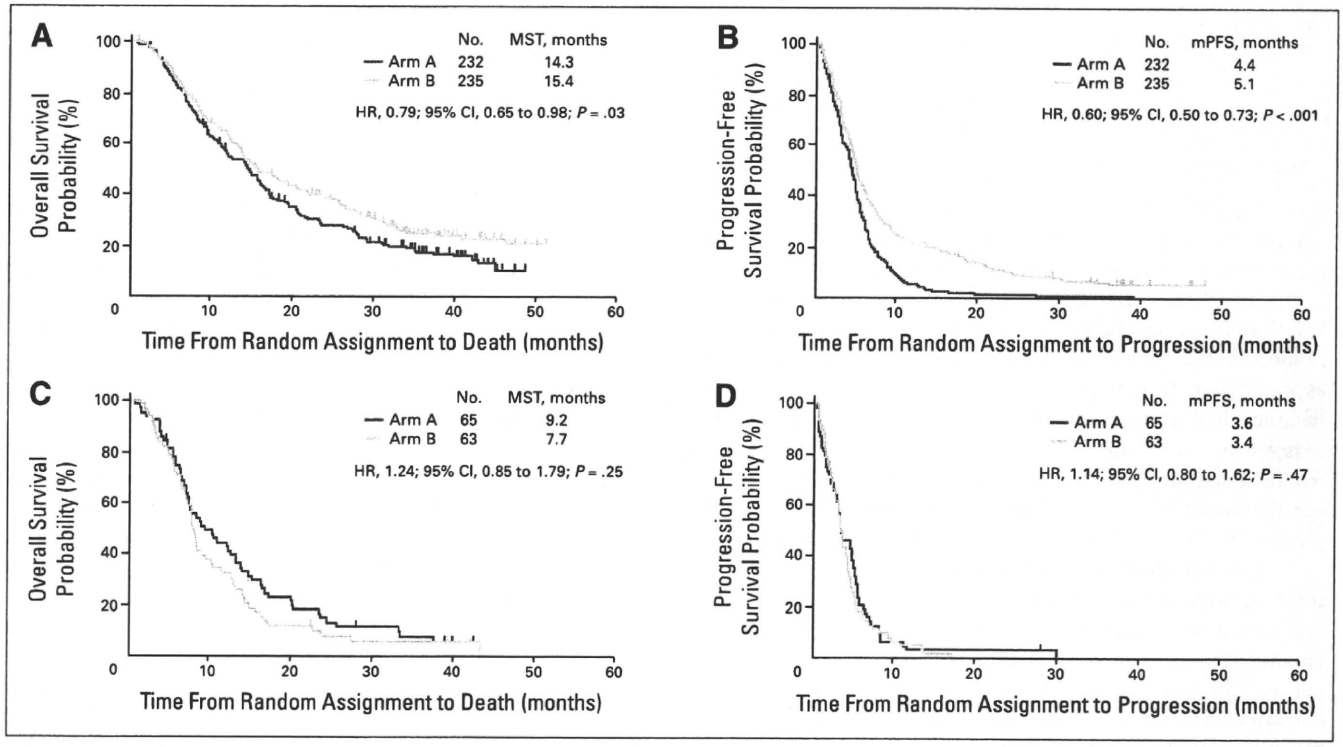

Fig 4. (A) Overall survival in the subset groups of patients with adenocarcinoma (n = 467), (B) progression-free survival in the subset groups of patients with adenocarcinoma (n = 467), (C) overall survival in the subset groups of patients with nonadenocarcinoma (n = 128), and (D) progression-free survival in the subset groups of patients with nonadenocarcinoma (n = 128). MST, median survival time; HR, hazard ratio; mPFS, median progression-free survival.

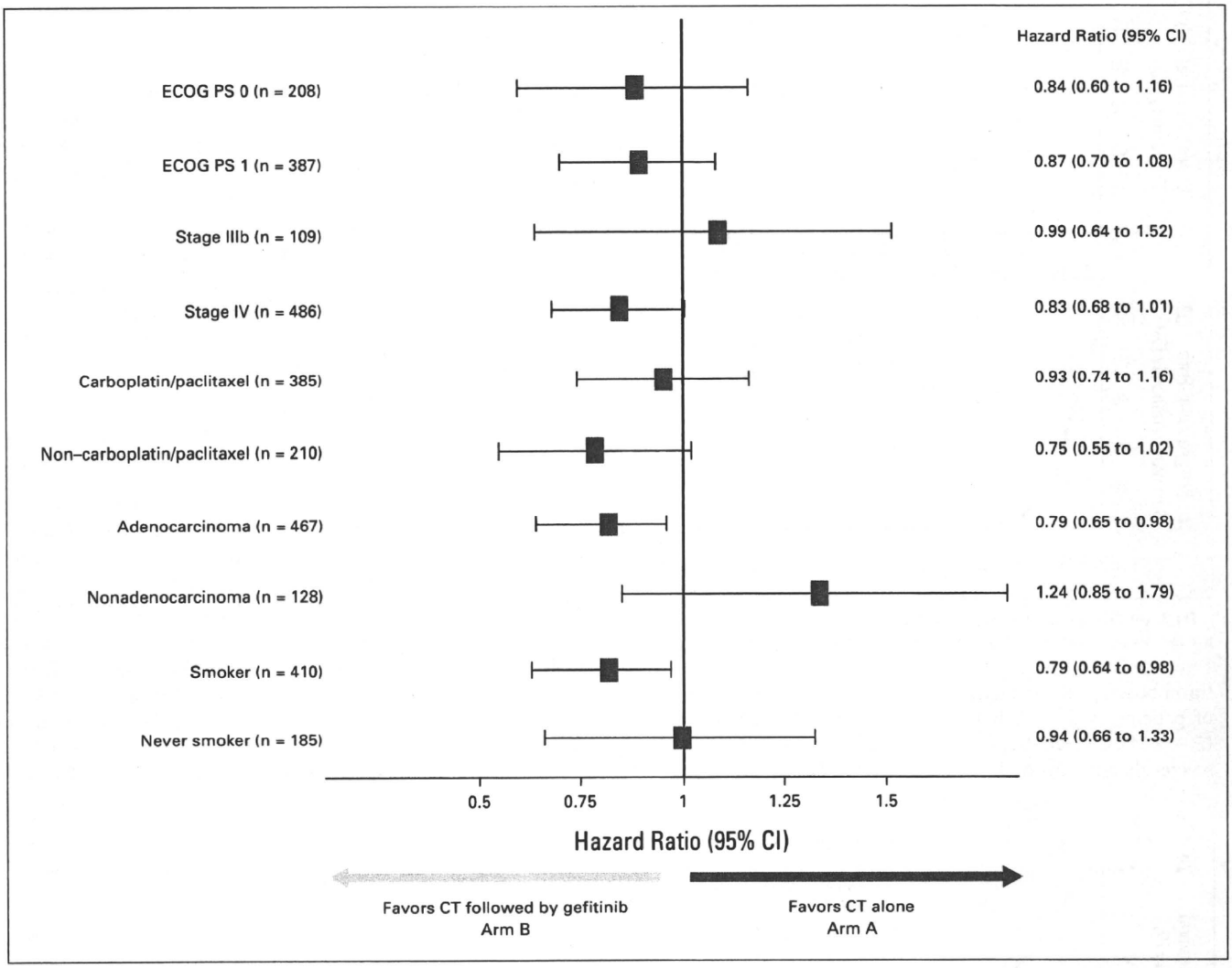

Fig 5. Forest plot subgroup analysis according to patients' backgrounds. CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status.

It was the first randomized, double-blind, placebo controlled trial to demonstrate a significant OS prolongation for maintenance treatment with pemetrexed in patients with advanced NSCLC (HR, 0.79; 95% CI, 0.65 to 0.95; $P = .012$).[22] The results of the Sequential Erlotinib in Unresectable NSCLC (SATURN) study, which was a randomized, double-blind, placebo controlled trial with erlotinib as maintenance, were presented this year. Erlotinib maintenance treatment had improvement in PFS of 41% compared with placebo.[23] Maintenance or sequential chemotherapy strategy after standard treatment has lately been receiving considerable attention. As a result, our trial was considered a consolidation therapy using other agent without progression after front-line treatment rather than maintenance.

Although the median number of chemotherapy cycles was three in both arms, 47.5% of patients received more than four cycles in Arm A. The number of treatment cycles was lower in Japanese than in whites; however, comparability was to be kept between the two arms in this randomized trial. These results were consistent with Japanese data on the median number of cycles of platinum-doublet chemotherapy.[15]

Toxicity results were consistent with previous Japanese studies of advanced NSCLC patients who received platinum-doublet chemotherapy.[15,16] Furthermore, no significant severe adverse events were seen that were not predictable from the safety profiles of gefitinib in sequential therapy after platinum-doublet chemotherapy. Recently published data suggested that gefitinib might be associated with ILD in Japanese patients[11]; however, in our study, the overall incidence of ILD was less than 1%, and no imbalance was identified between the two treatment arms in terms of ILD.

It was interesting that sequential gefitinib therapy had a significant survival prolongation in patients with adenocarcinoma histology (HR, 0.79; 95% CI, 0.65 to 0.98; $P = .03$). There was no difference also in PFS or OS for patients with nonadenocarcinoma. It was possible that these patients just did not benefit from an ineffective therapy of sequential gefitinib. In patients with NSCLC, adenocarcinoma histology, nonsmoker, and Japanese or Asian ethnicity are favorable predictive factors for a response to gefitinib treatment.[11-14] When the analysis was performed in the most favorable subset population that responded to gefitinib—that is, among those with both adenocarcinoma histology and nonsmokers—the MST was 23.5 months in arm A and 25.1 months and in arm B, respectively. Indeed, more than three quarters of the patients with favorable profiles in arm A received gefitinib after the protocol treatment, because physicians recognized

Table 2. Toxicity According to National Cancer Institute Common Toxicity Criteria Version 2

Toxicity	Arm A (n = 298)				Arm B (n = 300)				χ^2 Test *P* for Grade 3 + 4
	Grade 3		Grade 4		Grade 3		Grade 4		
	No.	%	No.	%	No.	%	No.	%	
Hematologic									
Leukopenia	98	32.9	21	7.0	97	32.3	14	4.7	.461
Neutropenia	90	30.2	136	45.6	79	26.3	133	44.3	.153
Febrile neutropenia	33	11.1	5	1.7	38	12.8	0	0	.297
Anemia	57	19.1	8	2.7	35	11.7	5	1.7	.006
Thrombocytopenia	32	10.7	0	0	18	6.0	1	0.3	.054
Nonhematologic									
Anorexia	43	14.4	0	0	33	11.0	2	0.7	.316
AST/ALT	11	3.7	1	0.3	32	10.7	0	0	.002
Constipation	25	8.4	0	0	20	6.7	1	0.3	.631
Creatinine	1	0.3	0	0	0	0	0	0	.315
Diarrhea	6	2.0	0	0	5	1.7	0	0	.152
Dyspnea	3	1.0	5	1.7	4	1.3	5	1.7	.816
Fatigue	22	7.4	7	2.3	18	6.0	4	1.3	.294
Hypersensitivity	1	0.3	1	0.3	2	0.7	2	0.7	.417
Infection	36	12.1	1	0.3	26	8.7	0	0	.135
Nausea	38	12.8	0	0	29	9.7	0	0	.232
Neuropathy									
Motor	5	1.7	1	0.3	4	1.3	1	0.3	.991
Sensory	12	4.0	1	0.3	7	2.3	0	0	.260
Performance status	27	9.1	8	2.7	23	7.7	9	3.0	.676
Pneumonitis (ILD)	2	0.7	0	0	4	1.3	0	0	.417
Rash	2	0.7	0	0	1	0.3	0	0	.559
Stomatitis/pharingitis	0	0	0	0	2	0.7	0	0	.482
Vomiting	12	4.0	1	0.3	15	5.0	2	0.7	.465

Abbreviation: ILD, interstitial lung disease.

these patients were more likely to respond to gefitinib. Patients who were nonsmokers with adenocarcinoma in arm A resulted in subsequent gefitinib therapy as well as in arm B.

Activating mutations in the gene for *EGFR* appear in a subset of adenocarcinoma of lung cancer.[24,25] A higher response to EGFR-TKIs is noted in specific subgroups that include females, never smokers, patients with adenocarcinoma histology, and East Asians.[12] Higher EGFR mutation rates are also noted in these subgroups and are also related to a better response to EGFR-TKIs[24,25] and longer survival.[12] Patients with these mutations exhibit objective response rates in the range of 75% to 95%.[12-14,26,27]

Patients included in this study were not selected on the basis of the target *EGFR* mutation status, because when this study was planned, we had not recognized the *EGFR* mutation as a predictive factor to respond to gefitinib. In Japanese patients with adenocarcinoma, a higher incidence of *EFGR* mutations, are estimated compared with white patients. It seems that more than 40% of Japanese patients with adenocarcinoma have an *EGFR* mutation.[12] Complex results in this study can be explained by analyzing the *EGFR* mutation status of participating patients. It may be important to select patients who are known to receive a clinical benefit with treatment using an EGFR-TKI.

In conclusion, this trial failed to meet the primary end point of OS in patients with advanced NSCLC. The exploratory subset analyses demonstrate a possible survival prolongation for sequential therapy of gefitinib, especially for patients with adenocarcinoma. Further investigations are warranted to confirm the best sequential therapy after platinum-based chemotherapy for patients with advanced NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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ORIGINAL REPORT

Phase III Study Comparing Second- and Third-Generation Regimens With Concurrent Thoracic Radiotherapy in Patients With Unresectable Stage III Non–Small-Cell Lung Cancer: West Japan Thoracic Oncology Group WJTOG0105

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Clinical Trials repository link available on JCO.org.

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ABSTRACT

Purpose
This phase III trial of concurrent thoracic radiotherapy (TRT) was conducted to compare third-generation chemotherapy with second-generation chemotherapy in patients with unresectable stage III non–small-cell lung cancer (NSCLC).

Patients and Methods
Eligible patients received the following treatments: A (control), four cycles of mitomycin (8 mg/m^2 on day 1)/vindesine (3 mg/m^2 on days 1, 8)/cisplatin (80 mg/m^2 on day 1) plus TRT 60 Gy (treatment break for 1 week); B, weekly irinotecan (20 mg/m^2)/carboplatin (area under the plasma concentration-time curve [AUC] 2) for 6 weeks plus TRT 60 Gy, followed by two courses of irinotecan (50 mg/m^2 on days1, 8)/carboplatin (AUC 5 on day1); C, weekly paclitaxel (40 mg/m^2)/carboplatin (AUC 2) for 6 weeks plus TRT 60 Gy, followed by two courses of paclitaxel (200 mg/m^2 on day1)/carboplatin (AUC 5 on day 1).

Results
The median survival time and 5-year survival rates were 20.5, 19.8, and 22.0 months and 17.5%, 17.8%, and 19.8% in arms A, B, and C, respectively. Although no significant differences in overall survival were apparent among the treatment arms, noninferiority of the experimental arms was not achieved. The incidences of grade 3 to 4 neutropenia, febrile neutropenia, and gastrointestinal disorder were significantly higher in arm A than in arm B or C ($P < .001$). Chemotherapy interruptions were more common in arm B than in arm A or C.

Conclusion
Arm C was equally efficacious and exhibited a more favorable toxicity profile among three arms. Arm C should be considered a standard regimen in the management of locally advanced unresectable NSCLC.

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INTRODUCTION

Lung cancer remains the leading cause of cancer-related deaths worldwide.[1] Non–small-cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases, and approximately 30% of patients with NSCLC present with locally advanced lung cancer.[2]

The standard treatment for stage III locally advanced NSCLC was a combined modality of thoracic radiotherapy (TRT) and chemotherapy.[3,4] Phase III studies have also been conducted to assess the efficacy and toxicity of concurrent chemoradiotherapy in comparison with that of sequential chemoradiotherapy. In two studies (ie, a Japanese report[5] and the RTOG9410[6]) that employed older, second-generation regimens, the survival period was reported to be significantly prolonged by concurrent chemoradiotherapy, although the toxicity was worse. Thus the standard of treatment for stage III locally advanced lung cancer is currently recognized as concurrent chemoradiotherapy.

During the last decade, the usefulness of several new agents, such as paclitaxel, gemcitabine, vinorelbine, and docetaxel, have been studied, usually administered in combination with the platinum compounds. These newer-agent/platinum combinations, the so-called third-generation regimens, have been proven to be more effective than

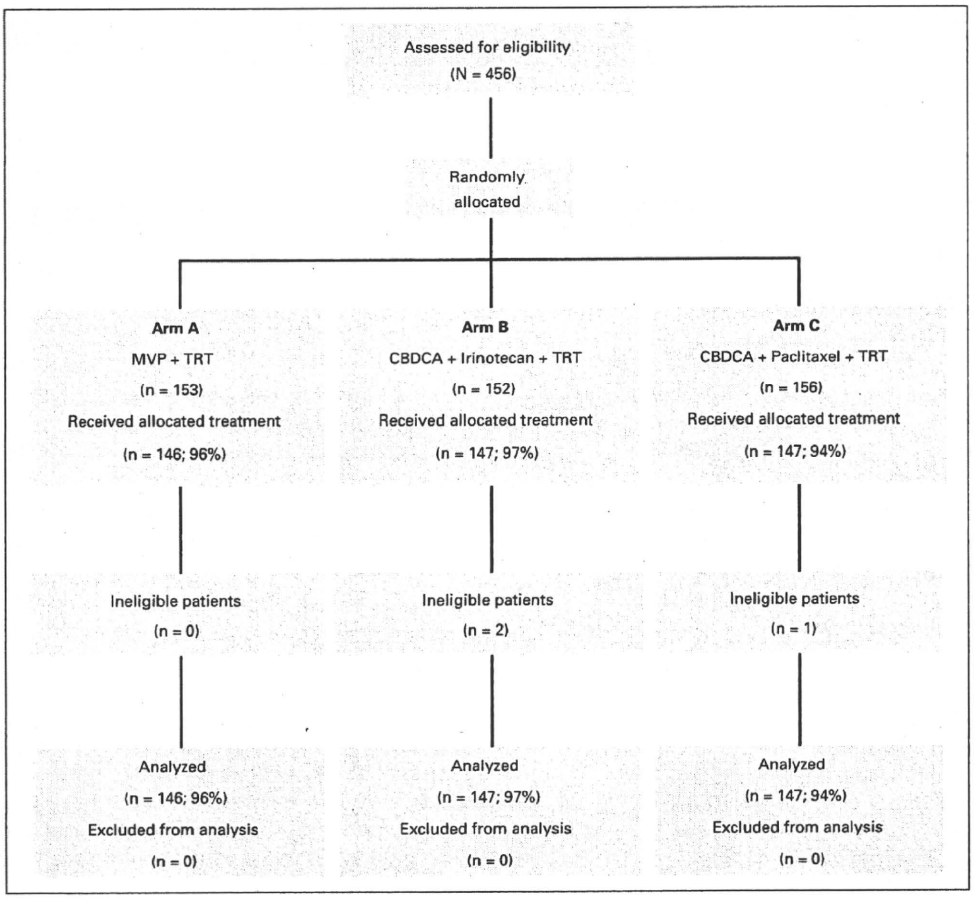

Fig 1. CONSORT diagram. MVP, mitomycin, vindesine, and cisplatin; TRT, thoracic radiotherapy; CBDCA, carboplatin.

second-generation regimens, as demonstrated by the increased survival of patients with metastatic NSCLC treated with these regimens.[7-9]

Because the chemotherapy regimens used in the above-described two reports were second-generation regimens, the benefit of the introduction of third-generation regimens for chemoradiotherapy has begun to be assessed. Although concurrent administration of full-dose chemotherapy and thoracic radiotherapy has been reported to be possible by some investigators, it is considered difficult for many regimens[10,11]; third-generation agents can hardly be used at their full doses for concurrent chemoradiotherapy because of the high incidence of toxicity associated with these agents. Therefore, for concurrent chemotherapy with TRT, these chemotherapeutic agents have been used at reduced doses in several reported clinical studies.[12-14] However, some reports have suggested that the marked efficacy of concurrent chemoradiotherapy using third-generation chemotherapeutic agents can hardly be achieved using these agents at reduced doses.[15]

However, it remains to be clearly established regarding which would be superior in terms of both the efficacy and toxicity: concurrent chemoradiotherapy using the second-generation regimens at full doses or the third-generation regimens at reduced doses. We, the West Japan Thoracic Oncology Group, therefore performed a phase III study to compare these therapeutic strategies. The doses of the chemotherapeutic agents were determined based on the results of Japanese phase I studies.[16,17]

PATIENTS AND METHODS

Patient Selection

Patients with histologically or cytologically confirmed NSCLC with unresectable stage III disease were assessed for eligibility (see CONSORT diagram, Fig 1). Unresectable stage IIIA disease was defined by the presence of multiple and/or bulky N2 mediastinal lymph nodes on computed tomography (CT), which rendered, in the opinion of the treating investigator, the patients unsuitable as candidates for surgical resection. Eligible patients also needed to meet the following criteria: measurable disease of 20 mm or more; no prior history of chemotherapy or TRT; Eastern Cooperative Oncology Group performance status $\leq$ 1; age $\leq$ 75 years; leukocytes $\geq$ 4,000/μL, platelets $\geq$ 100,000/μL, and hemoglobin $\geq$ 9.5 g/dL, serum creatinine $\leq$ institutional upper limit of normal, 24-hour creatinine clearance $\geq$ 60 mL/min, bilirubin $\leq$ 1.5 mg/dL, AST and ALT $\leq$ 2.0$\times$ upper limit of normal, and partial pressure of arterial oxygen $\geq$ 70 mmHg.

Patients were excluded if they had pulmonary fibrosis; other active, invasive malignancies in the 3 years leading up to protocol entry; malignant effusion; pyrexia of 38°C or more at baseline; infections; significant cardiac disease; uncontrolled diabetes mellitus; paresis of the intestine ileus; or regular use of corticosteroids. The institutional ethics committee of each of the participating institutions approved the protocol, and all patients provided written informed consent before the start of the study.

For staging, all patients underwent CT of the thorax, including the upper abdomen, and either a brain CT or brain magnetic resonance imaging. A radioisotopic bone scan was also performed for all patients. Positron emission tomography was not obtained in any of the enrollees at baseline.

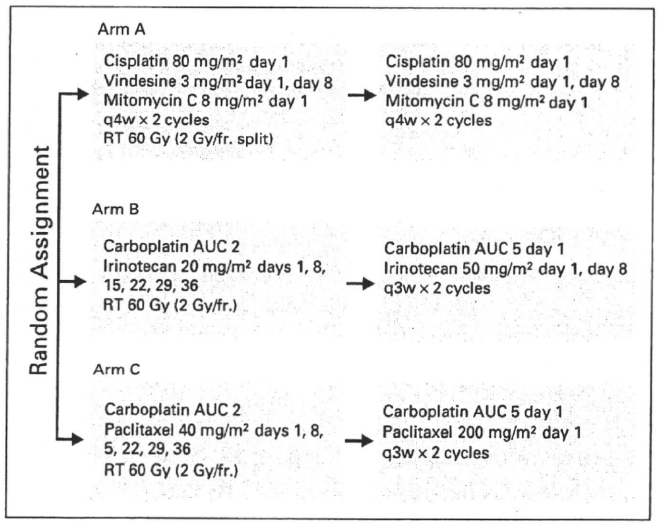

Fig 2. Treatment schema. q4w, every 4 weeks; RT, radiotherapy; fr, fraction; AUC, area under the plasma concentration-time curve.

Treatment Schedules

Patients were randomly assigned to one of the three following treatment arms (Fig 2). Treatment was composed of concurrent chemoradiotherapy and subsequent consolidation chemotherapy.

In arm A, chemotherapy consisted of vindesine 3 mg/m^2 on days 1 and 8, cisplatin 80 mg/m^2 on day 1, and mitomycin 8 mg/m^2 on day 1. This chemotherapy was repeated every 4 weeks, and four courses were administered. On day 2 of chemotherapy, TRT was begun at the dose of 2 Gy/fraction given in 15 fractions over 3 weeks, followed by a rest period of 1 week. Subsequently, radiation was again resumed at the dose of 2 Gy/fraction given in 15 fractions over 3 weeks. The total dose of radiation administered was 60 Gy.

In arms B and C, concurrent chemoradiotherapy was undertaken with the agents administered at reduced doses weekly for 6 weeks, followed by full-dose chemotherapy during the consolidation phase. The consolidation phase chemotherapy, initiated 3 to 4 weeks after the concurrent chemoradiotherapy, was administered in two cycles. TRT was initiated on day 1 at the dose of 2.0 Gy daily, five times per week. The total dose of 60 Gy was given in 30 fractions over a 6-week period.

The concurrent-phase chemotherapy consisted of irinotecan 20 mg/m^2 followed by carboplatin area under the plasma concentration time curve (AUC) 2 mg/mL/min in arm B and paclitaxel 40 mg/m^2 followed by carboplatin AUC 2 mg/mL/min in arm C. The consolidation chemotherapy consisted of 3-week cycles of irinotecan (50 mg/m^2 on days 1 and 8)/carboplatin (AUC 5 mg/mL/min on day 1) in arm B and paclitaxel (200 mg/m^2 administered over 3 hours) followed by carboplatin (AUC 5 mg/mL/min on day 1) in arm C.

Radiation Therapy

All patients were treated with a linear accelerator photon beam of 4 MV or more. The primary tumor and involved nodal disease received 60 Gy in 2-Gy fractions over 6 weeks in arms B and C and 7 weeks in arm A.

At the start of this multi-institutional study, three-dimensional (3D) treatment planning system using CT was not available at all institutions. Therefore, two-dimensional (2D) treatment planning techniques were allowed, and 3D dose constraints for both planning target volume and normal-risk organs were not determined in the protocol. Radiation doses were specified at the center of the target volume. In 2D treatment planning, doses were calculated assuming tissue homogeneity without correction for lung tissues, whereas lung inhomogeneity correction was performed in 3D treatment planning. Among 412 patients who received ≥ 54 Gy (arm A, n = 139; arm B, n = 137; and arm C, n = 136), 2D and 3D treatment planning was performed for 200 and 212 patients, respectively.

The initial 40 Gy was delivered to clinical target volume 1 (CTV1), and the final 20 Gy was delivered to a reduced volume defined as clinical target volume 2 (CTV2). CTV1 included the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal (no. 2) to subcarinal lymph nodes (no. 7). The contralateral hilum was not included in CTV1. The supraclavicular areas were not to be treated routinely, but could be treated when supraclavicular nodes were involved. For the primary tumors and the involved lymph nodes of 1 cm in the shortest diameter, a margin of 1.5 to 2 cm was added. CTV2 included only the primary tumor and the involved lymph nodes with a margin of 0.5 to 1 cm. The spinal cord was excluded from the fields for CTV2 by appropriate methods, such as the oblique opposing method. Appropriate planning target volume margin and leaf margin were added for CTV1 and CTV2. When grade 4 hematologic toxicity, grade 3 to 4 esophagitis or dermatitis, pyrexia of ≥ 38°C, or a partial pressure of arterial oxygen of less than 60 mmHg occurred, the TRT was interrupted.

Evaluation of Response and Toxicity

All eligible patients who received any treatment at all were considered as assessable for response and toxicity. Chest x-rays, CBCs, and blood chemistry studies were repeated once a week during the treatment period. Thoracic CT was performed once a month during the treatment period. After the treatment, thoracic CT was obtained every 3 months, and other imaging examinations were obtained when recurrence was suspected. The response was evaluated in accordance with Response Evaluation Criteria in Solid Tumors (RECIST). In the evaluation of the antitumor effects, extramural review was conducted. Overall survival (OS) was defined as the time from registration until death from any cause. Progression-free survival (PFS) was defined as the time between random assignment and disease progression, death, or last known follow-up. OS and PFS were estimated by the Kaplan-Meier method.

Statistical Analysis

The primary end point of this study was comparison of the OS between the control group (arm A) and each of the treatment groups (arm B or C). It was projected that the control group would achieve a median OS time of 16.5 months,[5] whereas the treatment group would show an increase in the median OS to 20.5 months, on the basis of previously published data.[14] When the upper limit of the adjusted CI of the hazard ratio of the control group to each treatment group was low 1.176 (1/0.85), the results were recognized as demonstrating noninferiority of the experimental treatment to the control treatment. The sample size was calculated assuming a 2.5% one-sided type I error and 80% power. The patient accumulation period was 4.5 years, and the follow-up period was 3 years. In view of the possibility of variance inflation owing to censoring, the sample size was set at 450 patients.

Baseline characteristics were compared among the treatment groups using the Kruskal-Wallis test for continuous variables and Fisher's exact test for discrete variables. Rates of occurrence of specific toxicities and treatment delivery were compared among the groups using Fisher's exact test.

RESULTS

Patient Characteristics

From September 2001 to September 2005, a total of 456 patients were registered for the study, and 153, 152, and 151 patients were allocated to arms A, B, and C, respectively. Of the total, 16 patients (arm A, n = 7; arm B, n = 5; arm C, n = 4) did not receive the protocol treatment because they were deemed ineligible for the study before the start of treatment after registration in five patients (large irradiation area, n = 2; stage IIB, n = 1; stage IV, n = 2), worsening of the underlying disease in four patients, worsening of complications in five patients, patient refusal in one patient, and unknown reason in one patient. The safety and antitumor effects of the treatments were eventually assessed on the basis of the data of 440 patients after exclusion of these 16 patients from the total of 456 patients enrolled. After the start of the treatment, three patients were found to be ineligible because of stage IV disease, but the data of these patients were included in all the analyses.

Table 1. Patient Characteristics

Characteristic	Arm A No.	Arm A %	Arm B No.	Arm B %	Arm C No.	Arm C %	P
Sex							.879
Female	18	12.3	21	14.3	19	12.9	
Male	128	87.7	126	85.7	128	87.1	
Age, years							.378
Median	63.0		62.0		63.0		
Range	31-74		30-74		38-74		
≥ 70	27	18.5	36	24.5	31	21.1	
Smoking history							.240
Absence	17	11.6	15	10.2	9	6.1	
Presence	129	88.4	132	89.8	138	93.9	
Performance status							.447
0	56	38.4	66	44.9	65	44.2	
1	90	61.6	81	55.1	81	55.1	
Unknown	0	0.0	0	0.0	1	0.7	
Weight loss during the previous 6-month period							.680
< 5%	92	63.0	100	68.0	95	64.6	
≥ 5%	28	19.2	24	16.3	29	19.7	
Unknown	26	17.8	23	15.6	23	15.6	
Staging							.901
IIIA	49	33.6	46	31.3	49	33.3	
IIIB	97	66.4	101	68.7	98	66.7	
N status							—
N2	94	64.4	86	58.5	99	67.3	
N3	33	22.6	43	29.3	32	21.8	
Histology							—
Adenocarcinoma	58	39.7	69	46.9	62	42.2	
Squamous cell carcinoma	70	47.9	62	42.2	71	48.3	

There were no statistically significant differences among the three arms in terms of patient characteristics (Table 1).

Treatment Administered

Table 2 shows the status of implementation of chemotherapy. During the concurrent phase, 40.8% of patients in arm B and 58.5% of patients in arm C received six weekly cycles of chemotherapy ($P = .003$); 67.3% of patients in arm B and 87.8% patients in arm C completed at least five cycles ($P < .001$). In regard to the consolidation phase, 41.1%, 29.3%, and 49.7% in arms A, B, and C, respectively, received the two scheduled courses of therapy ($P = .002$). Chemotherapy interruptions were more common in arm B than in arms A and C in both the concurrent and consolidation phases.

Table 2. Chemotherapy Administered

Chemotherapy Cycles	No. of Patients Arm A	Arm B	Arm C	P
Concurrent chemotherapy cycles				
1	18.5	0.7	2.0	
2	81.5	2.0	2.0	
3		5.4	1.4	
4		24.5	6.8	
5		26.5	29.3	B *v* C: .003
6		40.8	58.5	B *v* C: < .001
Consolidation chemotherapy				
0	46.6	34.0	30.6	
1	12.3	36.7	19.7	
2	41.1	29.3	49.7	A *v* B *v* C: .002

In most of the patients, TRT at 60 Gy was completed, and 6.8%, 8.2%, and 8.8% of patients in arms A, B, and C, respectively, received a radiation dose of less than 60 Gy. The reason for the reduced radiation dose was toxicity in two thirds of the patients (three patients from arm A; six patients from arm B, including two cases of esophagitis and two cases of pneumonitis; and seven patients from arm C, including one case of esophagitis and two cases of pneumonitis).

Toxicity

Table 3 lists the grade 3 or worse severe toxicities. There were a total of 11 treatment-related deaths. The cause of death was radiation pneumonitis in one patient and sepsis in one of the two patients in arm A; meningitis in one patient, pneumonia in one patient, radiation pneumonitis in two patients, and mycosis in one of the five patients in arm B; and radiation pneumonitis in three patients and death from other cause in one of the four patients in arm C. The clinical course of the patients who died of radiation pneumonitis are presented next. One patient from arm A developed pneumonitis on day 2 of the fourth course of treatment. In this patient, the pneumonitis subsided temporarily in response to corticosteroid therapy, but it aggravated again subsequently, resulting in death. In arm B, one patient developed pneumonitis after 54 Gy of TRT and died despite mechanical ventilation, and another patient developed pneumonitis at the end of the concurrent phase. In the latter patient, the pneumonitis subsided temporarily in response to pulsed corticosteroid therapy, but it aggravated again, resulting in death. In arm C, two patients developed pneumonitis at the end of the concurrent phase. Another patient from arm C developed pneumonitis on day 16 of the concurrent phase.

The incidences of grade 3 or worse severe hematologic toxicity, infection, febrile neutropenia, and gastrointestinal toxicity were significantly higher in arm A than in arm B or C. The incidence of grade

Table 3. Grade 3 or Worse Toxicity

Toxicity	All Treatment Arm A	Arm B	Arm C	P	Concurrent Phase Arm A	Arm B	Arm C	P
Neutropenia	95.9	60.5	61.9	< .001	93.8	53.7	23.1	< .001
Leukopenia	96.6	75.5	66.0	< .001	95.9	72.1	46.9	< .001
Anemia	25.3	17.7	8.8	< .001	15.8	8.8	6.1	0.019
Thrombocytopenia	28.8	28.6	7.5	< .001	21.9	11.6	5.4	< .001
Febrile neutropenia	37.0	8.8	10.2	< .001	30.8	6.1	3.4	< .001
Nausea	21.9	4.8	4.8	< .001	21.9	3.4	3.4	< .001
Vomiting	6.8	2.7	0.7	.012	6.2	1.4	0.0	.001
Fatigue	13.0	6.1	4.8	.019	9.6	2.0	1.4	< .001
Constipation	11.6	6.1	2.7	.009	8.9	6.1	1.4	.015
Diarrhea	0.7	2.0	1.4	.606	0.7	0.7	0.7	.999
Neurogenic (sensory)	0.7	0.7	4.8	.017	0.0	0.0	0.0	—
Esophagitis	5.5	2.7	8.2	.121	4.1	2.0	7.5	.077
Infection	26.0	16.3	17.0	.066	22.6	12.2	10.2	.006
Dyspnea	6.2	5.4	6.1	.957	2.7	0.7	2.0	.406
Pneumonitis	1.4	4.1	4.1	.312	0.0	0.0	0.7	.368

Table 4. Objective Response

Response	Arm A (n = 146)		Arm B (n = 147)		Arm C (n = 147)	
	No.	%	No.	%	No.	%
CR	3	2.1	4	2.7	5	3.4
PR	94	64.4	79	53.7	88	59.9
SD	16	11.0	32	21.8	32	21.8
PD	19	13.0	19	12.9	16	10.9
NE	14	9.6	13	8.8	6	4.1
Response rate, CR + PR*	97	66.4	83	56.5	92	63.0

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated.
*P = .198.

3 or worse severe neurogenic toxicity was significantly higher in arm C as compared with that in the other two arms. There were no statistically significant differences in the incidences of esophagitis, dyspnea, or pneumonitis, which are manifestations of radiation-related toxicity, among the three groups. The incidence of grade 2 or worse severe esophagitis was significantly higher in arm C (20.5%, 23.1%, and 33.3% from arms A, B and C, respectively; P = .003).

Efficacy

The objective response rates were 66.4%, 56.5%, and 63.3% in arms A, B, and C, respectively (Table 4). The response rates in arms B and C were not statistically significantly different from the rate in arm A.

The OS and PFS are shown in Figure 3. Most of the patients had been observed for more than 3 years, and 343 patients had died. The median survival time and 3- and 5-year survival rates in arm A were 20.5 months, 35.3%, and 17.5%, respectively. The corresponding values were 19.8 months, 24.2%, and 17.8% in arm B, and 22.0 months, 26.4%, and 19.5% in arm C. There was no statistically significant difference in the OS between arm B or C and arm A (arm A *v* B, P = .392; arm A *v* C, P = .876). The upper limits of the adjusted CI of the hazard ratio between arm A and B (1.402) or C (1.204) exceeded 1.176. Thus the results did not show noninferiority of the three experimental regimens (arm B and C) as compared with the reference treatment (arm A).

The OS was not significantly different according to sex (male, female), stage (IIIA, IIIB), and weight loss (< 5%, ≥ 5%) among the three arms. The causes of death after the third year are disease progression (n = 15, 6, and 9 in arms A, B, and C, respectively) and other disease (n = 3, 1, and 0 in arms A, B, and C, respectively).

The median PFS was 8.2, 8.0, and 9.5 months in arms A, B, and C, respectively. There was also no statistically significant difference of the PFS between arm B or C and A (arm A *v* B, P = .466; arm A *v* C, P = .621).

DISCUSSION

To our knowledge, this is the first phase III trial designed for direct comparison between second-generation and third-generation regimens applied in combination with concurrent TRT in patients with locally advanced lung carcinoma. This study was additionally aimed at comparing a cisplatin-based regimen with a carboplatin-based regimen and also more frequent radiosensitizing doses during TRT with systemic doses of chemotherapy during radiotherapy. In regard to chemotherapy for advanced lung cancer, a previous meta-analysis demonstrated that a cisplatin-based regimen is superior to a carboplatin-based regimen in terms of OS. In the present study, however, the OS in arm A (cisplatin-based regimen) was not significantly longer than that in arm B or C (carboplatin-based regimen). The observed intergroup differences possibly reflect the differences between the second- and third-generation regimens or between more frequent radiosensitizing doses and systemic doses of chemotherapy. In any event, the results of this study suggest that the third-generation

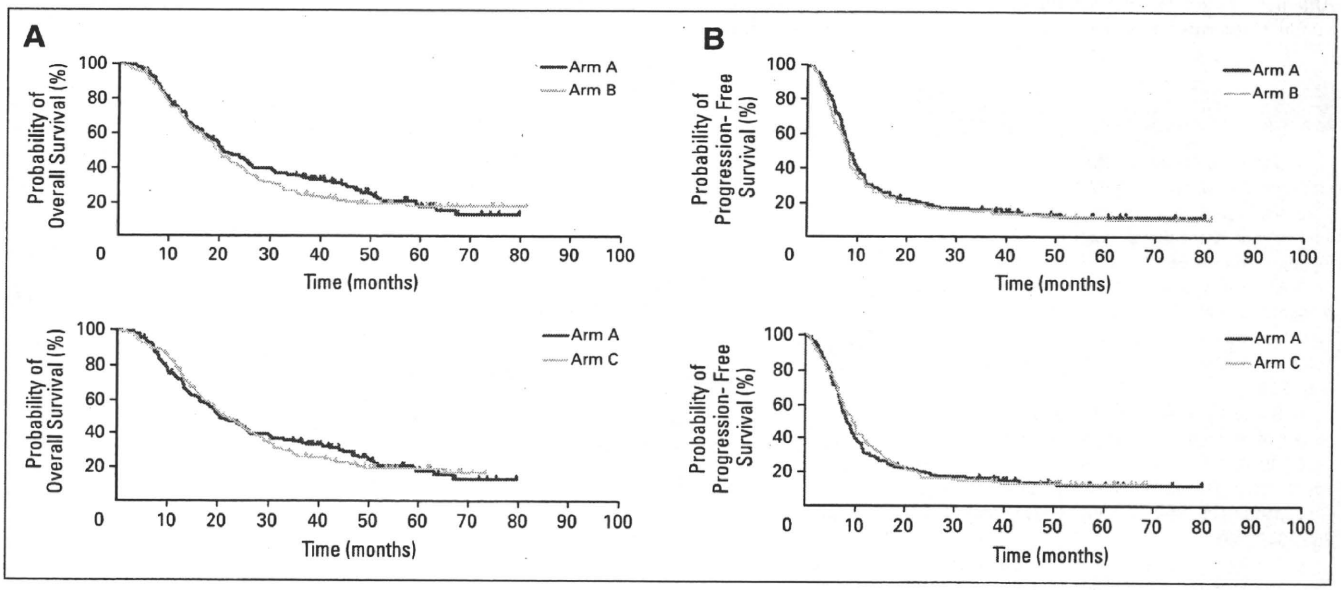

Fig 3. (A) Comparison of overall survival among the three randomly assigned arms. (B) Comparison of progression-free survival among the three randomly assigned arms.

carboplatin regimen (particularly carboplatin plus paclitaxel) was at least comparable to the second-generation cisplatin regimen, which is the conventionally used therapeutic regimen, in terms of the survival-prolonging effect when applied in combination with concurrent thoracic radiotherapy.

Unfortunately, noninferiority of OS was not demonstrated in the present study, probably because the number of the patients in this study resulted in a deficiency of power, because the therapeutic outcome in the reference arm was more favorable than that in conventional reports. The therapeutic outcome in the reference arm in recent phase III studies of chemoradiotherapy was more favorable than the estimated numerical data.[18] The favorable data may be attributable to bias as a result of the patient inclusion criteria or the development of radiotherapy, but no distinct cause could be identified.

Although noninferiority in terms of OS was not demonstrated in this study, the survival curves themselves mostly coincided among the three groups, as shown in Figure 2. The hematologic and gastrointestinal toxicities noted in arm A were significantly serious as compared with those in the experimental arms. Although the incidence of grade 3 or worse severe neurotoxicity was significantly higher, most of the other toxicities were the mildest in arm C among the three groups. Between the experimental arms, the rate of implementation of chemotherapy tended to be lower for arm C than for arm B. It was considered, from the viewpoint of feasibility, that arm C may be superior to arm B.

From these data on the efficacy and toxicity, we judged that concurrent chemoradiotherapy involving the combined use of carboplatin plus paclitaxel and TRT yielded the best results among the three groups, and we, the West Japan Thoracic Oncology Group, will select this treatment method as the reference arm for phase III studies in the future.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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