Table I. *Patients' characteristics.*

	Docetaxel + carboplatin c (%) (n=60)	Paclitaxel + arboplatin (%) (n=30)
Age (median) (years)	67.5	65.5
Male/female	43/13 (78/22)	22/8 (73/27)
Body weight loss>5% Yes /no	11/49 (18/82)	5/25 (17/83)
Performance status 0/1	19/41 (32/68)	7/23 (23/77)
Histology Sq/Ad/La/Other	13/36/2/9 (22/60/3/15)	10/17/0/3 (33/57/0/10)
Stage IIIB/IV	24/36 (40/60)	10/20 (33/67)
Naïve/relapsed	53/7 (88/12)	26/4 (87/13)
LDH Normal/abnormally high	44/16 (73/27)	21/9 (70/30)
Prior radiotherapy	3 (5)	3 (10)

Sq: Squamous cell carcinoma, Ad: adenocarcinoma, La: large cell carcinoma, LDH: lactate dehydrogenase.

Table II. *Overall response and survival data.*

Regimen	Docetaxel + carboplatin	Paclitaxel + carboplatin
Number of patients	60	30
Response rate (95%CI)	23% (13-36%)	33% (17-53%)
Median PFS (95% CI), months	4.8 (3.9-7.2)	5.1 (4.4-6.4)
PFS rate (90% CI)*	42% (31-52)	40% (25-54)
HR (95% CI)	0.86 (0.55-1.36)	Referent
Median OS (95% CI), months	17.6 (10.2-23.0)	15.5 (9.4-20.8)
HR (95% CI)	0.77 (0.47-1.26)	Referent
1-Year survival rate (90% CI)	60% (49-70)	60% (44-73)

MST: Median survival time, CI: confidence interval, HR: hazard ratio, PFS: progression-free survival , OS: overall survival. *At six months.

Table III. *Toxicities experienced during study period.*

Toxicity	Docetaxel+ carboplatin % (95% CI) N=60	Paclitaxel+ carboplatin % (95% CI) N=30
Grade 3 or more Neutropenia	88 (77-95)	60 (41-77)
Grade 3 or more Anemia (hemoglobin)	12 (5-23)	7 (1-22)
Grade 3 or more Thrombocytopenia	0	3 (0-17)
Grade 3 or more Frbrile neutropenia	17 (8-29)	13 (4-31)
Grade 2 or more Nausea	28 (18-41)	17 (6-35)
Grade 2 or more Vomiting	12 (5-23)	10 (2-27)
Grade 2 or more Sensory neuropathy	3 (0-12)	37 (20-56)
Grade 2 or more Myalgia	0	13 (4-31)
Grade 2 or more Arthralgia	2 (0-9)	20 (8-39)
Possible TRD (ARDS)	1	0

CI: Confidence interval, TRD: treatment-related death, ARDS: acute respiratory distress syndrome.

or time to progression was 4.8, 5.8, and 4.5 months, and the MST was 13.3, 14.1, and 12.3 months, respectively. These results are similar to those of the present trial, obtaining a PFS of 5.1 months and an MST of 15.6 months, and suggest that Japanese patients have a good response to taxane-based chemotherapy. C1236T polymorphism in the ATP-binding cassette sub-family B member-1 (*ABCB1*) gene is significantly related to docetaxel clearance (18). Gandara *et al.* reported ethnic differences in the metabolism of taxanes between American and Japanese patients with lung cancer in a common-arm analysis of PCarbo, performed jointly in the United States and Japan (19).

Differences in the allelic distribution of genes involved in paclitaxel disposition or DNA repair [cytochrome *P450* 3A4 (CYP3A4)*1B and excision repair cross-complementation group 2 (*ERCC2*) K751Q] were observed between Japanese and American patients. Resulting metabolic differences in taxane metabolism may consequently contribute to better outcomes in Asian patients with lung cancer who receive taxanes.

In our study the dose of docetaxel was 60 mg/m^2 and that of carboplatin was AUC 6 mg/ml min. This dose of docetaxel is generally used in Japan to treat NSCLC. When combined with cisplatin, the dose of docetaxel used in Japan may be slightly lower the one that used in other countries (6). However, the results of Japanese studies in terms of PFS or overall survival are not inferior to those of studies performed in other countries, where docetaxel is usually given at a dose of 75 mg/m^2 (7). On the other hand, most Japanese studies have used cisplatin at a dose of 80 mg/m^2, which is slightly higher than that used in other countries (75 mg/m^2). The modest differences in the doses of chemotherapeutic agents may not have had a major influence on PFS or overall survival. Brunetto *et al.* reported that the dose intensity of platinum-doublet regimens including cisplatin or carboplatin with either vinorelbine or gemcitabine did not have an impact on survival or time-to-progression in patients with NSCLC (20).

A phase III study comparing DCarbo with PCarbo as first-line chemotherapy was performed in 1,077 patients with ovarian cancer (21). Docetaxel (75 mg/m^2) or paclitaxel (175 mg/m^2) with carboplatin to (AUC 5 mg/ml min) was administered every three weeks for six cycles.

The study also concluded that DCarbo is similar to PCarbo in terms of PFS and response, but recommended that longer follow-up is required before making a definitive statement on survival. DCarbo was considered an alternative first-line regimen for chemotherapy in patients with ovarian cancer. As for toxicity, DCarbo was associated with

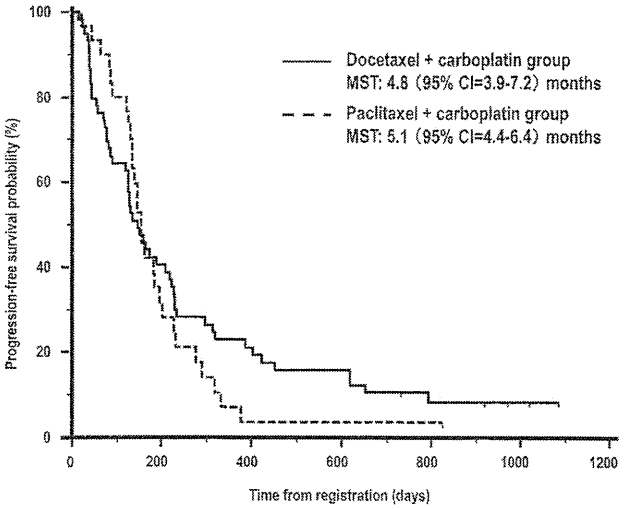

Figure 2. *Progression-free survival. MST: Median survival time, CI: confidence interval.*

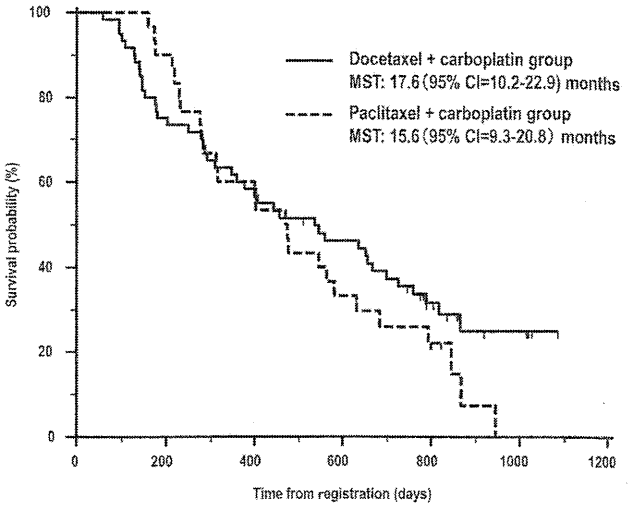

Figure 3. *Overall survival. MST: Median survival time, CI: confidence interval.*

substantially less overall and grade 2 or more neurotoxicity than PCarbo. On the other hand, DCarbo led to a higher incidence of grade 3 or 4 neutropenia than did PCarbo. Similar trends were noted in our study: DCarbo had a lower incidence of grade 2 or more sensory neuropathy (3% *vs.* 37%), but a higher incidence of grade 3 or more neutropenia (87% *vs.* 60%) as compared with PCarbo. Although myelosuppression was also frequently associated with DCarbo in our study, this adverse effect was not dose-limiting.

Recently, the survival of patients with NSCLC has improved, in part because of improved treatments or perhaps because of selection bias. The longer the survival, the more problematic is chronic toxicity such as neurotoxicity. Such toxicity negatively affects the quality of life of patients with NSCLC. This is especially true for those tested with PCarbo regimens (22). Even if the dose of paclitaxel is reduced from 225 mg/m^2 to 200 mg/m^2, the problem of neurotoxicity persists. DCarbo would, thus, be the preferred regimen to avoid severe neurotoxicity.

The treatment-related death in the DCarbo group in our study was reviewed by a safety committee. ARDS occurred as late as two months after the end of the patient's fifth, final cycle of treatment. The relation of death to chemotherapy with DCarbo was considered not definite, but possible.

Our study had several important limitations. We studied only Japanese patients, and it remains unclear whether our results can be extrapolated to other ethnic groups. Our study group comprised of patients with all histological types of NSCLC, and information on mutations in the *EGFR* gene was not obtained. In addition, the doses of docetaxel and carboplatin differed from those used in Western studies of patients with NSCLC.

Conclusion

Docetaxel plus carboplatin is considered an alternative first-line chemotherapeutic regimen for patients with newly-diagnosed advanced NSCLC, at least in Asia. In the future, this regimen might be combined with other treatments, such as molecular targeted therapy.

Conflicts of Interest

None.

Acknowledgements

We are indebted to the late Kiyoyuki Furuse, MD, who contributed to the data management of this study.

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Received July 18, 2013
Revised September 13, 2013
Accepted September 16, 2013

JJCO Japanese Journal of Clinical Oncology

Original Articles

Jpn J Clin Oncol 2014;44(2)116–121
doi:10.1093/jjco/hyt195
Advance Access Publication 13 December 2013

A Feasibility Study of Carboplatin Plus Irinotecan Treatment for Elderly Patients with Extensive Disease Small-cell Lung Cancer

Yuki Misumi[1,*], Makoto Nishio[2], Toshiaki Takahashi[3], Fumiyoshi Ohyanagi[2], Atsushi Horiike[2], Haruyasu Murakami[3], Hirotsugu Kenmotsu[3], Nobuyuki Yamamoto[3], Mari Ishii[1], Tsuneo Shimokawa[1], Naoya Hida[1] and Hiroaki Okamoto[1]

[1]Department of Respiratory Medicine and Medical Oncology, Yokohama Municipal Citizen's Hospital, Kanagawa, [2]Department of Respiratory Medicine, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo and [3]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan

*For reprints and all correspondence: Yuki Misumi, Department of Respiratory Medicine and Medical Oncology, Yokohama Municipal Citizen's Hospital, 56 Okazawa-cho, Hodogaya-ku, Yokohama, Kanagawa 240-8555, Japan. E-mail: yu00-misumi@city.yokohama.jp

Received September 2, 2013; accepted November 17, 2013

Objective: The role of platinum agents plus irinotecan has been unclear for elderly patients with extensive disease small-cell lung cancer. We conducted a feasibility study to evaluate the safety and efficacy of carboplatin plus irinotecan in preparation for a planned Phase III study.
Methods: Based on another Phase I study, carboplatin area under the curve of four Day 1 plus irinotecan 50 mg/m^2 Days 1 and 8 every 3 weeks for four courses was administered. Patients aged ≥70 years with a performance status of 0–2 were eligible. The primary endpoint was feasibility, defined as the percentage of patients who have received three or more courses of chemotherapy. If the feasibility was ≥60% in the first 10 patients, this endpoint would be considered to be met.
Results: Eleven patients were registered. The median age was 77 years, and nine patients had a performance status of 1. Ten patients completed four courses of treatment, and neither dose omission nor modification was required. The feasibility was 91% (10/11) and the relative dose intensity was 76.9%. Because neutropenia was frequently prolonged, the next course was delayed in 53% of all courses. Other toxicities were generally mild, and the only Grade 4 toxicity was hyponatremia. The overall response rate was 90% (9/10), and the progression-free survival and the overall survival were 5.1 and 10.9 months, respectively.
Conclusions: This regimen appears to be feasible and effective. Based on these results, a Phase II/III trial comparing carboplatin plus etoposide with carboplatin plus irinotecan for elderly patients with extensive disease small-cell lung cancer is being planned by the Japan Clinical Oncology Group.

Key words: chemo-respiratory tract – chemo-Phase I–III – clinical trials – lung medicine

INTRODUCTION

Approximately 30–40% of patients with small-cell lung cancer (SCLC) are ≥70 years old, and the proportion of elderly SCLC patients is continuously increasing in Japan (1–3). However, as elderly patients have been frequently excluded from clinical trials, no standard chemotherapeutic regimen has been established for this patient population. Moreover, standard chemotherapeutic regimens for non-elderly SCLC patients are not always suitable for older patients due to their vulnerable organ function and/or co-morbidities. Therefore, the establishment of a chemotherapeutic regimen that is well balanced between safety and efficacy for this population should be pursued.

The Japan Clinical Oncology Group (JCOG) 9702 study compared carboplatin plus etoposide (CE) versus split-dose cisplatin plus etoposide (SPE) in elderly and poor-risk patients with extensive disease (ED)-SCLC (4). Based on the results of this study, the JCOG concluded that the SPE regimen should remain as the standard treatment for elderly and poor-risk patients with ED-SCLC, the CE regimen being an alternative. However, because the CE regimen does not require hydration and can be administered in an outpatient setting, elderly patients with ED-SCLC in Japan more commonly receive this regimen.

In contrast, the Phase III JCOG 9511 study has shown that irinotecan plus cisplatin (IP) is more effective than etoposide plus cisplatin (EP) for treating non-elderly patients with ED-SCLC (5). However, elderly patients (age ≥71 years) were excluded from this trial. When considering the treatment plan for elderly patients with ED-SCLC, the 1-day bolus administration of this cisplatin-based regimen would be difficult because hydration is required. Until now, the carboplatin plus irinotecan (CI) regimen has been repeatedly reported. Although several studies included patients 70 years of age or older, few studies were especially designed for the elderly. Therefore, it would be meaningful to consider a CI regimen for the elderly. Two randomized trials have compared CI with CE for ED-SCLC patients. Although Schmittel et al. (6) did not show a significant survival benefit in the CI arm, survival was marginally better and fewer hematological toxicities were observed. In contrast, Hermes et al. (7) reported a significant survival advantage of CI over CE. Although these trials were not specifically designed for elderly patients and the doses used differed from Japanese standard doses, we believed it was worthwhile to investigate the efficacy of CI in elderly patients with ED-SCLC. Furthermore, a recent meta-analysis of camptothecins compared with etoposide in combination with platinum in ED-SCLC showed a survival benefit associated with camptothecins plus platinum (excluding nogitecan) over etoposide plus platinum in a subgroup analysis (8). Thus, a Phase III trial comparing CE with CI in elderly patients with ED-SCLC is being warranted in the JCOG Lung Cancer Study Group (LCSG).

In our previous study (9), we reported the 4-weekly schedule of CI regimen using prophylactic granulocyte colony-stimulating factor (G-CSF) support in elderly patients with SCLC. However, this study was not a Phase I study and had a heterogeneous patient population. In addition, because not only chemotherapy-naïve but also pretreated patients were included and the treatment drug dose was changed according to the patient's characteristics, the recommended dose could not be decided in the study. Recently, prophylactic use of G-CSF has not been preferred in clinical practice in Japan because more expensive cost and prolonged hospital stays are required. For the reason given above, we cannot apply the previous data to plan the Phase III study and we think that optimal schedule and dose of CI for elderly patients with SCLC have not been established. On the other hand, Thoracic Oncology Research Group (TORG) decided a recommended dose of 3-weekly schedule of CI regimen for elderly patients with limited disease (LD)-SCLC in a Phase I study (unpublished data). Because thoracic radiotherapy was sequentially administered after four courses of chemotherapy in this Phase I study, it might be justified that the recommended dose of CI for LD-SCLC could be used in elderly patients with ED-SCLC based on these data. Furthermore, because members of JCOG and TORG were much different, JCOG-LCSG recommended a further feasibility study by only JCOG members for elderly patients with ED-SCLC. Therefore, we conducted a feasibility study to evaluate the safety and efficacy of CI in elderly patients with ED-SCLC in preparation for a future JCOG Phase III study designed to compare CE with CI in this patient population. This study is registered with the UMIN Clinical Trials Registry as trial 000003208.

PATIENTS AND METHODS

Patient Selection

Patients with the following inclusion criteria were enrolled: age ≥70 years; cytologically or histologically confirmed SCLC; ED stage (defined as at least one of the following: distant metastasis, contralateral hilar-node metastasis, malignant pleural effusion and pericardial effusion); no prior chest radiotherapy or chemotherapy; an Eastern Cooperative Oncology Group performance status (PS) of 0–2; no other co-existing malignancy and adequate hematologic, hepatic and renal organ function (leukocyte count ≥4000/mm^3, absolute neutrophil count [ANC] ≥2000/mm^3, platelet count ≥100 000/mm^3, hemoglobin level ≥9.0 g/dl, aspartate aminotransferase [AST]/alanine aminotransferase [ALT] levels ≤2× upper limit of normal range, total bilirubin ≤1.5 mg/dl, creatinine ≤1.5 mg/dl, creatinine clearance ≥50 ml/min and PaO_2 ≥ 60 mmHg). The additional criteria were: no symptomatic pericardial or pleural effusion requiring drainage, no active concomitant malignancy, no senile dementia, no diarrhea and provision of written informed consent. The exclusion criteria included brain metastases requiring radiotherapy, superior vena cava syndrome requiring radiotherapy and serious medical or psychiatric illness. Patients with interstitial pneumonitis detected by chest computed tomography (CT) scan were excluded. All the patients had chest X-ray, CT scan of the chest and abdomen, CT scan or magnetic resonance imaging of the brain and isotope bone scanning or positron emission tomography within 28 days before registration.

Treatment Plan

Based on our previous feasibility study using CI for elderly patients with SCLC (9), the TORG conducted a Phase I study of the CI regimen and sequential thoracic radiotherapy for elderly patients with LD-SCLC. In that study, the recommended dose was carboplatin area under the curve (AUC) of four Day 1 and irinotecan 50 mg/m^2 Days 1 and 8 every 3 weeks (unpublished data). Although the TORG study

included only elderly patients with LD-SCLC, we elected to use the recommended dose from this study in the current study of elderly patients with ED-SCLC. Thus, all the patients were assigned to carboplatin AUC 4 intravenously (IV) on Day 1 plus irinotecan 50 mg/m^2 IV on Days 1 and 8 every 21 days. Irinotecan on Day 8 was withdrawn if leukocyte counts were $<3000/mm^3$, platelet counts were $<100\,000/mm^3$ or if diarrhea Grade ≥ 1 occurred. Treatment was repeated for up to four cycles. Subsequent cycles were permitted only if the ANC was $\geq 1500/mm^3$, the leukocyte count was $\geq 3000/mm^3$, the platelet count was $\geq 100\,000/mm^3$, serum creatinine was ≤ 1.57 mg/dl, AST/ALT levels were $\leq 2.5\times$ upper limit of normal range, PS was 0–2, neither infection nor fever was present and treatment-related non-hematologic toxicities (excluding alopecia) had resolved to Grade ≤ 2 after Day 21. A treatment delay of ≤ 2 weeks was permitted. Use of G-CSFs was recommended in accordance with their package inserts or clinical recommendations. If G-CSF therapy was administered, the criteria for the next cycle had to be satisfied both after Day 21 and ≥ 2 days after discontinuation of G-CSF. Antiemetic prophylaxis with 5-HT$_3$ antagonists plus dexamethasone was routinely administered. Dose modifications were allowed only once if Grade 4 leukopenia or neutropenia lasting ≥ 4 days, Grade 4 thrombocytopenia or Grade 3 non-hematological toxicities, except for nausea/vomiting, constipation, hyponatremia and creatinine, occurred. When dose modification was needed, the next treatment course was started with carboplatin AUC 4 on Day 1 plus irinotecan 40 mg/m^2 on Days 1 and 8 every 21 days.

The protocol treatment was terminated if any of the following occurred: disease progression, a treatment delay ≥ 2 weeks, need for dose modification two times, Grade 2–4 pneumonitis and Grade 4 non-hematological toxicities. Because this was a feasibility study, post-protocol treatments were left to the discretion of the treating physicians.

Study Design

This trial was designed as a multicenter prospective feasibility study. The study protocol was approved by the institutional review board at each institution prior to study initiation. The primary objective was feasibility, defined as the percentage of patients who have received three or more courses of chemotherapy. Patients showing disease progression prior to receiving three courses of chemotherapy were excluded from the feasibility evaluation. In addition, even if irinotecan was not administered on Day 8 due to toxicity, the chemotherapy course was judged as being complete. In the JCOG9702 (4), the percentages of patients who have received three and four courses of CE regimen were 69 and 63%, respectively. In this study, we considered that the completion rate of three or more courses of chemotherapy was a more appropriate endpoint than that of four courses because CI regimen might be more toxic than the CE regimen. Therefore, we concluded that the study treatment was feasible when the completion rate of three or more courses of chemotherapy was $\geq 60\%$. Ten patients were initially registered into this study. If the feasibility (completion rate) was $>60\%$, the study would be considered to have yielded positive results and to be finished. If the completion rate was 30 to $<60\%$, we planned to enroll 10 more patients to confirm whether the low rate was due to the treatment regimen or to chance. If the feasibility remained at $<60\%$ in a total of 20 patients, the study would be considered to have yielded negative results. The secondary objectives were toxicity status, overall response rate (ORR), progression-free survival (PFS) and overall survival (OS). Tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors criteria, version 1.0. Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria version 3.0.

If a patient was documented as having a complete response (CR) or a partial response (PR), a confirmatory evaluation was performed after an interval of at least 4 weeks. The patient was considered to have a stable disease (SD) if it was confirmed and sustained for 6 weeks or longer.

The relative dose intensity (RDI) of irinotecan was calculated by dividing the actual received dose of the agent among all chemotherapy courses (mg/m^2/week) by the total projected dose of the four treatment courses (mg/m^2/week). When chemotherapy was completed without any delays or skipping of agents, the RDI was 100%.

Table 1. Patient characteristics

Median age, years (range)	77.5 (70–82)
Gender	
Male/female	10/0
ECOG PS 0/1	1/9
TNM classification	
T 4/3/2/1	4/2/1/3
N 0/1/2/3	1/1/2/6
M 0/1	1/9
Brinkman index	
Median (range)	1110 (840–3000)

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

RESULTS

Patient Characteristics

From March 2010 through March 2011, 11 patients were registered in three institutions. One patient withdrew consent after Day1 of the first course. Because this patient did not experience acute toxicities and the reason seemed to be related to other personal problems, we thought one more additional patient to the previously scheduled 10 patients were appropriate for this study. The median age was 77 (range, 70–82) years and nine patients had a PS of 1, all of whom were male (Table 1). The median Brinkman Index was 1110 (range,

840–3000). A patient with M0 had a contralateral hilar lymph node metastasis.

Drug Delivery and Dose Intensity

Except for the one patient who withdrew consent, all the patients completed four courses of treatment and no omission of irinotecan on Day 8 occurred (Table 2). Furthermore, no patients required dose modifications. Because the completion rate was 91% (10/11), the primary endpoint of a ≥60% completion rate was met. The RDI of irinotecan was 76.9%. The median course delays between the first and second courses, second and third courses and third and fourth courses were 8.5 (range, 2–11) days, 5.5 (range, 0–10) days and 6.5 (range, 0–17) days, respectively. Of a total of 30 courses, the reasons for chemotherapy delay of ≥4 days were leukopenia or neutropenia in 15 patients (50%) and thrombocytopenia and leukopenia in one patient (3%). Delays caused by bed scheduling at participating institutions occurred in six cases (20%).

Toxicities

Toxicity profiles are shown in Table 3. Both hematological and non-hematological toxicities were generally mild. The only Grade 4 toxicity was hyponatremia in one patient. Grade 3 ANC, hemoglobin and thrombocytopenia occurred in six (60%), one (10%) and two (20%) patients, respectively. G-CSF was administered to three patients. No treatment-related deaths occurred during the study.

One patient suffered from pneumonia during his first course of chemotherapy. He received antibiotic therapy for 7 days and fully recovered. He did not experience infection in subsequent protocol treatment cycles.

Another patient suffered from Grade 4 hyponatremia (117 mEq/l) during his first course of chemotherapy. He did not have any history of renal dysfunction and was considered to have syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a paraneoplastic syndrome. Appropriate intravenous crystalloid infusion facilitated full recovery, and he was able to continue chemotherapy. Severe hyponatremia was not observed in his subsequent protocol treatment cycles.

Table 2. Additional days required in each course and the reasons for delays

Patient no.	Courses 1 and 2	Courses 2 and 3	Courses 3 and 4
1	+7[a]	+10[a]	+11[a]
3	+8[a]	+4[a]	+8[a]
4	+7[b]	+7[b]	+6[b]
5	+11[b]	+7[b]	0[d]
6	+11[a]	+4[a]	+7[a]
7	+8[c]	+9[b]	+2[d]
8	+9[a]	0[d]	+13[a]
9	+2[d]	0[d]	0[d]
10	+11[a]	+2[d]	+1[d]
11	+11[a]	+8[a]	+17[a]
Median delays (range)	8.5 (2–11)	5.5 (0–10)	6.5 (0–17)

Relative dose intensity = 76.9%.
[a]Leukocytopenia.
[b]No available bed.
[c]Leukocytopenia/thrombocytopenia.
[d]No delay or delay within 2 days.

Efficacy

Nine patients achieved PR and one patient experienced SD, yielding an ORR of 90%. The median PFS was 5.1 months (95% confidence interval [CI]: 3.9–5.8; Fig. 1), and the median OS was 10.9 months (95% CI: 7.6–16.8; Fig. 2).

Second-Line Therapy

A total of 9 patients received second-line chemotherapy. The most commonly administered agent was amrubicin ($n = 7$). Other regimens included nogitecan ($n = 1$) and CI ($n = 1$). Palliative chest radiotherapy was administered to one patient. Only one patient did not receive second-line chemotherapy, due to poor PS.

Table 3. Toxicity (worst of any course)

	Grade		
	2	3	4
Hematological			
Leukopenia	3	3	0
Neutropenia	2	6	0
Anemia	5	1	0
Thrombocytopenia	2	2	0
Non-hematological			
High AST/ALT	1	0	0
Creatinine	0	0	0
Nausea	2	0	0
Vomiting	0	0	0
Diarrhea	3	0	0
Constipation	1	0	0
Pneumonitis	0	0	0
Bleeding	0	0	0
Infection	0	1	0
Hyponatremia	0	0	1
Peripheral neuropathy	1	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

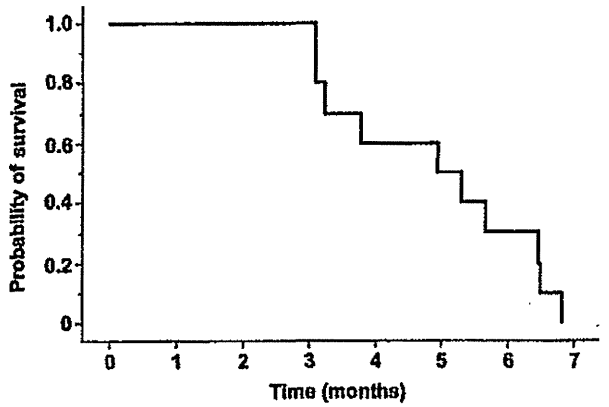

Figure 1. Progression-free survival. Median: 5.1 months (95% confidence interval [CI]: 3.9–5.8).

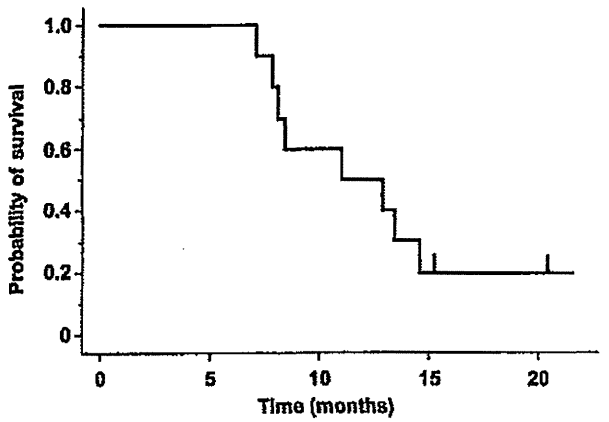

Figure 2. Overall survival. Median: 10.9 months (95% CI: 7.6–16.8).

DISCUSSION

Standard treatment for elderly patients with ED-SCLC has been controversial until now. Moreover, no global treatment consensus for these elderly patients has yet been reached. Because the median age of lung cancer patients is increasing in Japan, the need to formulate a strategy for treating this population is urgent. Some trials have shown that irinotecan might be a key drug for SCLC, particularly among Asian individuals (5,9); therefore, we conducted this feasibility study of CI in elderly SCLC patients. In this study, except for one patient who withdrew consent for chemotherapy, all other patients completed four courses of protocol treatment and the primary endpoint was met, with a feasibility of 91% (10/11). The toxicities were tolerable in this study. In general, Grade 4 hematologic toxicities are commonly experienced in association with chemotherapy for SCLC, even in patients with a good PS and adequate organ function (4–9). Only one patient in the present study experienced Grade 4 hyponatremia, and no Grade 4 hematologic toxicities were observed. The low frequency of diarrhea is particularly interesting. While the JCOG 9511 study comparing IP with EP (5) showed that the frequency of diarrhea associated with the IP regimen was relatively high (16%), no Grade 3 or 4 diarrhea was observed in the present study. Although the reason for this low frequency of diarrhea remains unclear, the low dose of irinotecan used (50 mg/m^2, Days 1 and 8) might have been a contributing factor.

While no CRs were observed, the 90% (9/10) response rate was satisfactory. Moreover, both OS and PFS were slightly longer than those observed in both treatment arms of JCOG 9702, which had almost the identical eligibility criteria (4). These data suggest that the CI regimen might improve outcomes of elderly patients with ED-SCLC. Two possible reasons may explain the promising efficacy observed in this trial. First, amrubicin was administered to 70% of patients as second-line chemotherapy. This agent was not administered at the time of the JCOG 9702 study. Because some investigators reported that second-line amrubicin was effective in relapsed SCLC (10–13), the use of this agent might have positively impacted on survival in this study. Secondly, all of the patients PS of 0–1, even though the eligibility criteria also allowed a PS of 2. In contrast, 26% of patients in the JCOG9702 study had a PS of 2–3 (4). Therefore, patient selection may have also contributed to the prolonged survival and reduced toxicities observed in this study.

This study has several limitations. First, we could have conducted more dose escalation due to the mild toxicity. However, chemotherapy delays occurred frequently, primarily due to neutropenia. Because dose escalation could have potentially caused more severe myelosuppression or delays of chemotherapy administration, we believe that it would have been difficult to escalate the dose in this trial. Secondly, our regimen included relatively low doses compared with the regimens used in non-elderly patients. Administration of irinotecan 50 mg/m^2 Days 1 and 8 every 3 weeks yields a dose intensity of 33 mg/m^2/week. In contrast, the dose intensity of irinotecan (60 mg/m^2, Days 1, 8 and 15, every 4 weeks) was 45 mg/m^2/week in JCOG9511. However, the omission of Day 15 irinotecan occurred in 50% of the courses in JCOG9511 (5). As no omission of Day 8 irinotecan occurred in the present study and course delays only occurred occasionally, the actual difference in dose intensity between the present trial and JCOG9511 may be relatively small. Thirdly, this feasibility study had a small sample size. Further investigation with a larger number of patients is warranted to verify the current results. Fourthly, this trial was not designed based upon an appropriate statistical method. However, if this study was done as a Phase II study using a Simon Minimax design, ~30–40 patients were required. At the time of study initiation, we felt that CI regimen became a promising experimental arm for a future Phase III trial based on our previous study. In addition, many JCOG members hesitated to perform a time-consuming Phase II trial of CI regimen. Therefore, we evaluated the feasibility of this regimen using a small sample size of 10 patients. If a marginal result for feasibility was obtained in the first 10 patients, additional 10 patients were required to avoid a negative result by chance.

In conclusion, treatment with CI in elderly ED-SCLC patients is feasible and appears to provide less toxicities and more efficacy than other regimens. Based on the current study, a Phase II/III trial comparing CE with CI in elderly patients with ED-SCLC is being scheduled by the JCOG LCSG.

Funding

This research was supported in part by National Cancer Center Research and Development Fund (23-A-18).

Conflict of interest statement

None declared.

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Histology and Smoking Status Predict Survival of Patients with Advanced Non–Small-Cell Lung Cancer

Results of West Japan Oncology Group (WJOG) Study 3906L

Yoshihito Kogure, MD, Masahiko Ando, MD,† Hideo Saka, MD,* Yasutaka Chiba, PhD,‡ Nobuyuki Yamamoto, MD, PhD,§ Kazuhiro Asami, MD,‖ Tomonori Hirashima, MD,¶ Takashi Seto, MD,# Seisuke Nagase, MD, PhD,** Kojiro Otsuka, MD, PhD,†† Kazuhiro Yanagihara, MD, PhD,‡‡ Koji Takeda, MD,§§ Isamu Okamoto, MD, PhD,‡ Takuya Aoki, MD, PhD,‖‖ Koichi Takayama, MD, PhD,¶¶ Masahiro Yamasaki, MD, PhD,## Shinzo Kudoh, MD, PhD,*** Nobuyuki Katakami, MD, PhD,††† Mikinori Miyazaki, MD, PhD,‡‡‡ and Kazuhiko Nakagawa, MD, PhD‡*

Introduction: Smoking status is one of the prognostic factors in advanced non–small-cell lung cancer (NSCLC). Currently, adenocarcinoma (Ad) histology is considered a predictive factor in advanced NSCLC. We investigated the correlation between histology or smoking status and survival of NSCLC patients receiving chemotherapy.

Methods: We retrospectively reviewed clinical data from stage IIIB or IV NSCLC patients who started first-line chemotherapy at affiliated institutions of West Japan Oncology Group from 2004 to 2005. We also collected information on pack-years of cigarette smoking and years since cessation. Overall survival was compared using log-rank test, and Cox regression analysis was used to identify independent prognostic factors.

Results: In total, 2542 consecutive patients were enrolled at 40 institutions. Of those, 71 were excluded because of unknown smoking history. The median overall survival of nonsmoking Ad patients (593 days) was longer than that of smoking Ad, nonsmoking non-Ad, and smoking non-Ad patients (384, 374, and 319 days, respectively; $p < 0.001$). In Cox regression with sex, age, stage, performance, and treatment as covariates, we found significant interaction ($p = 0.039$) between histology (Ad/non-Ad) and smoking status (smoker/nonsmoker); smoking conferred a hazard ratio of 1.34 (95% confidence interval, 1.15–1.55) in Ad, but only 0.99 (0.75–1.31) in non-Ad. Higher pack-years and shorter period since cessation were significantly associated with poorer survival in Ad ($p < 0.001$), but not in non-Ad ($p \geq 0.434$).

Conclusion: Ad histology is associated with better prognosis, and only smoking status had a prognostic impact in Ad.

Key Words: Non–small-cell lung cancer, Histology, Adenocarcinoma, Smoking status.

(*J Thorac Oncol.* 2013;8: 753–758)

*Department of Respiratory Medicine, National Hospital Organization, Nagoya Medical Center, Nagoya, Japan; †Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan; ‡Division of Biostatistics, ‡Department of Medical Oncology, Clinical Research Center, Kinki University School of Medicine, Osaka, Japan; §Thoracic Oncology Division, Shizuoka Cancer Center, Nagaizumi, Japan; ‖Department of Medical Oncology, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan; ¶Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino, Japan; #Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan; **Department of Thoracic Surgery, Tokyo Medical University, Tokyo, Japan; ††Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan; ‡‡Department of Translational Clinical Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; §§Department of Clinical Oncology, Osaka City General Hospital, Osaka, Japan; ‖‖Department of Internal Medicine, Division of Respiratory Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan; ¶¶Graduate School of Medical Sciences, Research Institute for Diseases of the Chest, Kyushu University, Fukuoka, Japan; ##Department of Respiratory Disease, Hiroshima Red Cross Hospital and Atomic Bomb Suvivors Hospital, Hiroshima, Japan; ***Department of Respiratory Medicine, Osaka City University Medical School, Osaka, Japan; †††Division of Integrated Oncology, Institute of Biomedical Research and Innovation Hospital, Kobe, Japan; and ‡‡‡Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Science, Nagoya, Japan.

This study is registered with University Hospital Medical Information Network-Clinical Trial Registry (UMIN-CTR) (http://www.umin.ac.jp/ctr/index.htm umin.ac.jp/ctr; identification number UMIN000001263).

Disclosure: Dr. Yanagihara has received grants from Taiho Pharmaceutical and Chugai Pharmaceutical. The other authors declare no conflict of interest.

Address for correspondence: Masahiko Ando, MD, Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya 466–8560, Japan. E-mail: mando@med.nagoya-u.ac.jp

ISSN: 1556-0864/13/0806-0753

Lung cancer is the leading cause of cancer-related mortality in Japan, and the rest of the world, with more than one million people dying from it each year. Non–small-cell lung cancer (NSCLC), which accounts for nearly 80% of all lung cancers, comprises several histological types, including adenocarcinoma (Ad), squamous cell carcinoma (Sq), and large-cell carcinoma (La). NSCLC had been treated as a single disease because of similar therapeutic effects of conventional chemotherapeutic agents. In the last few decades, however, treatment with new drugs, such as epidermal

growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), bevacizumab, and pemetrexed revealed that tumor histology has profound impact on the benefits of a variety of chemotherapy or targeted-therapy regimens for advanced NSCLC.[1–4] Thus, histology came to be considered a predictive factor for the effectiveness of specific chemotherapy in patients with advanced NSCLC. However, there is no previous report on histology as a prognostic factor, that is, a variable determining survival irrespective of the chemotherapy regimen administered.

Previous studies showed that cigarette smoking is an independent prognostic factor in patients with NSCLC,[2,5–7] but a dose–response relationship between the quantity of smoking and survival has not been established. Although Yelena et al.[6] noted that patients who had smoked up to 15 pack-years had a longer survival than those with more than a 15 pack-year history, other cutoff points for the amount of cigarette smoking have not been considered. In addition, the relationship between smoking and survival was not investigated with respect to differences in NSCLC histological subtypes, and the studies that did evaluate survival in Sq versus non-Sq patients did not reach a firm conclusion.[7,8] However, Kawaguchi et al.[8] showed that Ad had better prognosis than Sq in never-smokers, but not in ever-smokers, suggesting that the prognostic impact of cigarette smoking may differ among histologic subtypes in NSCLC.

We hypothesized that Ad histology and lower smoking status would result in better overall survival (OS) in advanced NSCLC. To test this hypothesis, we investigated the impact and possible interaction of histology and smoking status on survival of advanced NSCLC patients receiving chemotherapy in the clinic.

PATIENTS AND METHODS

Study Patients

We sent case report forms to 40 affiliated institutions of West Japan Oncology Group, and requested them to provide demographic and clinical data from medical records for all patients with stage IIIB or IV NSCLC, who started first-line systemic chemotherapy between January 1, 2004 and December 31, 2005. Patients who had a relapse after surgery or radiotherapy were excluded. The case report forms were submitted by the participating institutions during the period from September 2008 to January 2009. This study was approved by the institutional review board of each participating institution.

Demographic and Clinical Variables

We obtained the following baseline demographic and clinical information from the case report forms: age, sex, histology, disease stage, Eastern Cooperative Oncology Group performance status (PS), smoking status, type of first-line chemotherapy, number of treatment regimens, and the year in which first-line chemotherapy was started. Disease stage was determined according to the tumor, node, metastasis system.[9] Staging classification was performed by physical examination, chest–abdominal computed tomography, brain magnetic resonance imaging, bone scan, and positron emission tomography if necessary. Patients were categorized into nonsmokers and smokers according to smoking status. Nonsmokers were defined as those who had smoked less than 100 cigarettes. Among smokers, exsmokers were defined as those who had quit smoking 1 year or more before diagnosis, and current smokers as those who continued their smoking habit at diagnosis. Pack-years of smoking were calculated by multiplying the number of packs (20 cigarettes in one pack) smoked per day by the number of years smoked, and categorized as less than 10, 10 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59, and 60 or more. Years of smoking cessation were categorized as 1 to 4, 5 to 9, 10 to 14, 15 to 19, and 20 or more. Type of first-line chemotherapy was categorized into platinum-based combination, nonplatinum combination, and single-agent chemotherapy. Because the only approved EGFR-TKI for the treatment of inoperable or recurrent NSCLC in Japan before October 2007 was gefitinib, we collected information on gefitinib usage during the observation period and noted the starting day of gefitinib treatment. OS was calculated from the start of first-line chemotherapy to the date of death. Patients still alive were censored as of the last known follow-up.

TABLE 1. Patient Characteristics

Parameter	Ad (n = 1731)	Non-Ad (n = 740)	p
Men/women	1056/675	641/99	<0.001
Smoking status			<0.001
Nonsmoker	659	79	
Exsmoker	300	165	
Current smoker	772	496	
Stage IIIB/IV	444/1287	271/469	<0.001
PS			0.002
0	546	206	
1	873	402	
2	191	96	
3	90	25	
4	31	11	
Histology			—
Sq	—	516	
La	—	71	
Others	—	153	
Chemotherapy			0.181
Single-agent	354	137	
P doublet	1306	571	
Non-P doublet	71	32	
Regimen			<0.001
1	536	285	
2	445	201	
3	322	115	
≥4	428	139	
Gefitinib Y/N	959/772	146/594	<0.001

Ad, adenocarcinoma; PS, performance status; Sq, squamous cell; La, large cell; P, platinum; Y, yes; N, no.

Statistical Analysis

Demographic and clinical variables were compared among groups according to lung cancer histology, using the χ^2 test. The primary endpoint of this study was OS. Survival curves were calculated by the Kaplan–Meier method and compared using the log-rank test. Prognostic importance of histology and smoking status were analyzed using the Cox regression analysis adjusted for sex, age, disease stage, PS, type of first-line chemotherapy, and the year in which first-line chemotherapy was started. For detection of possible interaction between histology and smoking status, the terms of interaction of the two variables were evaluated by the likelihood ratio test. Because gefitinib was the preferred choice in patients with Ad, another Cox regression analysis was performed, in which patients were censored at the start of gefitinib administration, and the results were compared with the original Cox analysis. Significance level was set at a p value of 0.05. Statistical analyses were performed with SAS version 9.2 software (SAS Institute, Cary, NC).

RESULTS

Between January 1, 2004 and December 31, 2005, 2542 consecutively treated patients were enrolled at 40 institutions. Of these, 71 were excluded because of unknown smoking history. The characteristics of the study population, categorized into Ad and non-Ad, are listed in Table 1. There were 1731 Ad and 740 non-Ad patients (29.9% and 70.1%, respectively). Among them, we confirmed 1346 and 599 deaths in Ad and non-Ad patients, respectively. There were significantly more women (39.0% in Ad versus 13.4% in non-Ad) and nonsmokers (38.1% in Ad versus 10.7% in non-Ad) in the Ad group than in the non-Ad group. Patients who received single-agent chemotherapy accounted for approximately 20% of the study population. Compared with combination regimens, single-agent chemotherapy was associated with old age (63.6 years for combination regimens versus 71.1 years for single-agent chemotherapy), high proportions of female patients (29.3% versus 40.0%), nonsmokers (27.8% versus 34.0%), stage IV (69.4% versus 78.3%), and PS 0 to 1 (60.9% versus 87.1%). The proportion of Ad histology was not significantly different between single-agent and combination regimens (72.1% and 69.5%, respectively). The OS was 464 days in Ad compared with 326 days in non-Ad ($p < 0.001$; Fig. 1*A*). Between Ad and non-Ad, which was divided into Sq and La, Ad had significantly better survival than the other two histological groups (Sq, 341 days; La, 254 days; $p < 0.0001$; Fig. 1*B*). With regard

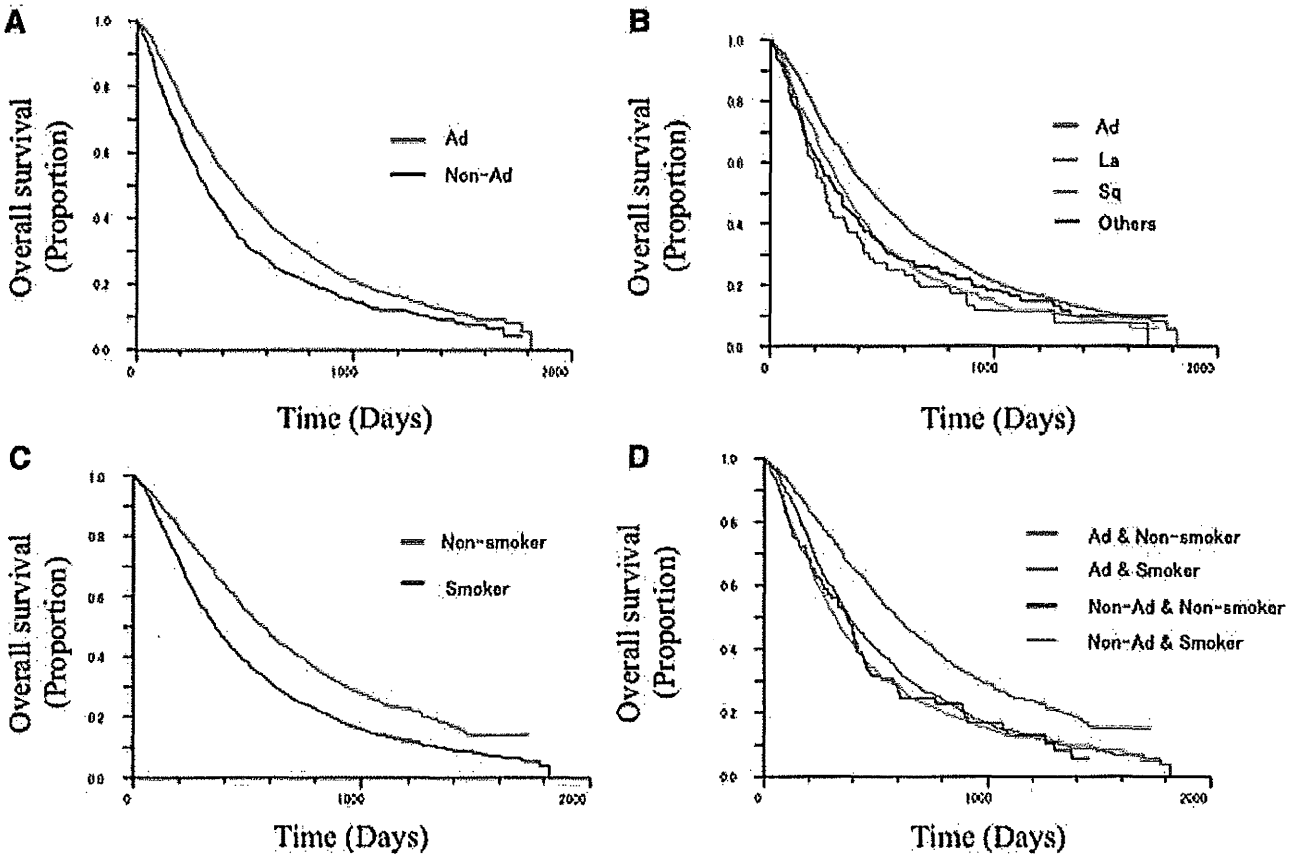

FIGURE 1. Kaplan–Meier plots of overall survival for patients classified according to histology type as (*A*) Ad and Non-Ad; histologic subtype as (*B*) Ad, La, Sq, and others; smoking status as (*C*) smokers and nonsmokers; and combination of smoking status and histology as (*D*) Ad and nonsmoker, Ad and smoker, Non-Ad and nonsmoker, and Non-Ad and smoker. Ad, adenocarcinoma; La, large cell; Sq, squamous cell.

TABLE 2. Survival Analysis by Cox Proportional Hazards Model (n = 2471)

Parameter	HR	95% CI	p
Sex			
Women	1		
Men	1.342	1.168–1.541	<0.001
Age yrs	1.007	1.002–1.012	0.005
Smoking status			
Nonsmoker	1		
Exsmoker	1.178	0.997–1.391	0.054
Current smoker	1.335	1.155–1.543	<0.001
Clinical stage			
Stage IIIB	1		
Stage IV	1.505	1.358–1.669	<0.001
PS			
0	1		
1	1.609	1.446–1.790	<0.001
2	2.229	1.910–2.601	<0.001
3	3.048	2.455–3.785	<0.001
4	5.487	3.864–7.790	<0.001
Histology			
Ad	1		
Sq	1.143	1.015–1.286	0.028
La	1.542	1.182–2.011	0.001
Others	1.397	1.159–1.683	<0.001
Chemotherapy			
Single-agent	1		
Non-P doublet	0.842	0.657–1.080	0.175
P doublet	0.793	0.699–0.899	<0.001

HR, hazard ratio, CI, confidence interval; PS, performance status; Ad, adenocarcinoma; Sq, squamous cell; La, large cell; P, platinum.

to smoking status, nonsmokers (568 days) had significantly longer survival than smokers (358 days; $p < 0.0001$; Fig. 1*C*). In a combined analysis of smoking status and histology, the median OS of Ad in nonsmokers was longer than that of Ad in smokers, non-Ad in nonsmokers, and non-Ad in smokers (593, 384, 374, and 319 days, respectively; $p < 0.001$; Fig. 1*D*). In Cox regression analysis, sex, age, smoking status, disease stage, PS, histology, and chemotherapy showed a statistically significant prognostic impact on survival (Table 2). When the interaction between histology (Ad/non-Ad) and smoking status (smoker/nonsmoker) was included in the Cox model, significant interaction was observed ($p = 0.039$); smoking conferred a hazard ratio (HR) of 1.34 (95% confidence interval [CI], 1.15–1.55) in Ad, in contrast to 0.99 (0.75–1.31) in non-Ad. In detailed analyses that excluded the 104 patients (current smokers, 89; unknown, 15) with unknown amount of cigarette smoking, shorter period since cessation showed a significant trend for poorer survival in the whole population ($p < 0.001$). This trend was also observed in Ad ($p < 0.001$; Table 3), but not in non-Ad ($p \geq 0.434$; Table 3). When non-Ad patients were divided into Sq and La or others, the trend p was 0.534 in Sq and 0.165 in La or others. The prognosis became significantly worse with higher pack-years of cigarette smoking in the whole population and Ad ($p < 0.001$; Table 3), but no significance was not achieved for the non-Ad group ($p = 0.519$; Table 3). When non-Ad patients were divided into Sq and La or others, the trend p was 0.798 in Sq and 0.380 in La or others. The prognostic impact of histology and smoking status remained significant in the Cox regression analysis, in which patients were censored at the start of gefitinib administration; positive smoking history, Sq histology, and La or other histology conferred an HR of 1.51 (95% CI, 1.21–1.88), 1.22 (95% CI, 1.06–1.41), and 1.59 (95% CI, 1.32–1.93), respectively. The negative prognostic impact of shorter period since cessation and pack-years of cigarette smoking was also essentially unchanged ($p < 0.001$ in both).

DISCUSSION

The consensus report of prognostic factors in NSCLC at the 1990 International Association for the Study of Lung Cancer Workshop showed that histology was not a prognostic factor for advanced NSCLC.[10] Our study is the first report to reveal that histology is a significant prognostic factor for advanced NSCLC. Importantly, we showed that Ad patients have the longest survival of all three histological groups (Ad, Sq, and La). Ad is the most common histological subtype of lung cancer in nonsmokers,[11] who have been reported to have a better prognosis than smokers.[12–14]

Smoking has been described as a prognostic factor in lung cancer. Although multiple studies have demonstrated the negative effects of smoking in patients with NSCLC, most included a heterogeneous population comprising patients with all stages and types of lung cancer.[5] In contrast, our study cohort consisted exclusively of patients with advanced NSCLC treated with first-line chemotherapy. We showed that smoking status is an independent prognostic factor for survival in those patients. Similar data have been shown in former studies.[2,5] However, those reports did not show whether smoking conferred any survival impact for advanced NSCLC irrespective of histological subtypes. In our study, only Ad histology had significant interaction with smoking status or smoking index and prognosis. A higher level of smoking was related to shorter survival in Ad patients, whereas smoking level and survival were not associated in non-Ad patients. Although the proportion of non-Ad patients was 29.9% of the total, the observed number of deaths in this study yielded a statistical power of more than 80% for detecting an HR of 1.5 at the 5% significance level in both Ad and non-Ad patients. Others have found that Ad histology is a significant prognostic factor in separate multivariate analysis for never-smokers in advanced NSCLC.[8] Yelena et al.[6] showed that high cigarette smoking, as measured in pack-years, is associated with decreased survival after diagnosis of stage IIIB/IV NSCLC. However, the patients of that study received a wide variety of therapies, raising the possibility that the outcomes might have been the result of distinct therapeutic responses. Although we only assessed the prognostic value of smoking status at diagnosis, assessment of smoking status at a later point, that is, at the time of treatment, would also have been of interest to determine whether cessation at the time of diagnosis leads to improved survival.

TABLE 3. Hazard Ratios According to Quantitative Aspects of Smoking

	Ad			Non-Ad		
	HR	95% CI	p	HR	95% CI	p
Years after cessation	(n = 1731)			(n = 740)		
Current	1.492	1.271–1.750	<0.001	1.204	0.849–1.707	0.297
Exsmoker 1–4 yr	1.438	1.114–1.857	0.005	1.101	0.733–1.653	0.643
Exsmoker 5–9 yr	1.549	1.101–2.180	0.012	1.228	0.700–2.155	0.474
Exsmoker 10–14 yr	1.127	0.783–1.621	0.520	1.235	0.680–2.245	0.488
Exsmoker 15–19 yr	1.199	0.761–1.890	0.433	1.410	0.712–2.794	0.325
Exsmoker ≥20 yr	0.873	0.834–1.203	0.407	1.103	0.662–1.837	0.706
Trend p	<0.001			0.434		
Pack-yr	(n = 1665)			(n = 702)		
<10	1.267	0.899–1.785	0.176	1.196	0.535–2.672	0.662
10–19	1.118	0.801–1.561	0.513	0.963	0.512–1.812	0.908
20–29	1.346	1.048–1.729	0.020	1.368	0.887–2.109	0.157
30–39	1.345	1.071–1.689	0.011	0.954	0.624–1.458	0.827
40–49	1.370	1.096–1.712	0.006	1.128	0.763–1.669	0.546
50–59	1.483	1.164–1.890	0.001	1.238	0.828–1.851	0.298
≥60	1.595	1.312–1.939	<0.001	1.135	0.791–1.628	0.491
Trend p	<0.001			0.519		

[a] Nonsmokers were set as the reference category.
Ad, adenocarcinoma; HR, hazard ratio; CI, confidence interval.

In agreement with the findings of another study,[15] we also found that a large proportion of Ad patients were nonsmoking. The prognostic difference between Ad in never-smokers and smokers may suggest that both are different disease entities. Of note, tumor-mutational frequencies and spectra suggest differences between smokers and nonsmokers.[16,17] However, significant differences in the frequency of somatic mutations in oncogenes such as *EGFR* and *KRAS* have been observed between smoking and nonsmoking lung cancer patients.[11] *EGFR* mutations, clinical predictors of EGFR-TKI therapeutic benefits, are more frequently found in nonsmoking Ad patients.[11] In another study, *EGFR* mutations were identified in nonsmokers (51%), former smokers (19%), and current smokers (4%).[18] Moreover, the incidence of *EGFR* mutations decreased with increasing number of pack-years of cigarette smoking.[18] However, *KRAS* mutations, predicting poor survival and resistance to EGFR-TKI, are more frequently found in smoking Ad patients. Interestingly, *EGFR* and *KRAS* mutations are mutually exclusive.[11]

Currently, therapeutic options other than EGFR-TKIs (e.g., bevacizumab and pemetrexed) are available in Japan. Still, NSCLC subtypes have been showing variable response rates and adverse events.[2,4,19,20] Non-Sq histology, especially Ad, is currently the NSCLC subtype with broader and more efficacious treatment options. At the time of this study, however, the only approved therapeutic agent for NSCLC in Japan was gefitinib. Unfortunately, we did not investigate *EGFR* mutation status. However, genetic background could possibly predict response to gefitinib. Along with its retrospective nature, this was a limitation of our study. However, we found that the treatment choice was made on the basis of clinical background, and we were unable to conclude whether or not gefitinib contributed to better survival under unknown *EGFR* mutation status. Hence, we suggest that decision-making based on clinical information alone is inappropriate. Both the V15-32 study[21] and the Iressa Survival Evaluation in Lung Cancer (ISEL) study[22], support our observations. Furthermore, the IRESSA Pan-Asia Study (IPASS) study,[23] conducted under the hypothesis that EGFR-TKI would be effective in clinically selected patients, confirmed the strong predictive value of *EGFR* mutations for the response of Ad to gefitinib.

This retrospective study has a few other limitations as well. First, information on smoking was not obtained from the interview or the self-administered questionnaire. Smoking data can be inaccurate, particularly when collected retrospectively. Second, we did not collect data on the procedures for histological diagnosis. The basis for pathological diagnosis is important because cytological assessment alone may lead to underdiagnosis of specific histologic types.

In conclusion, this survey demonstrated that Ad histology is associated with better prognosis, and that smoking status has a prognostic impact only in patients with Ad.

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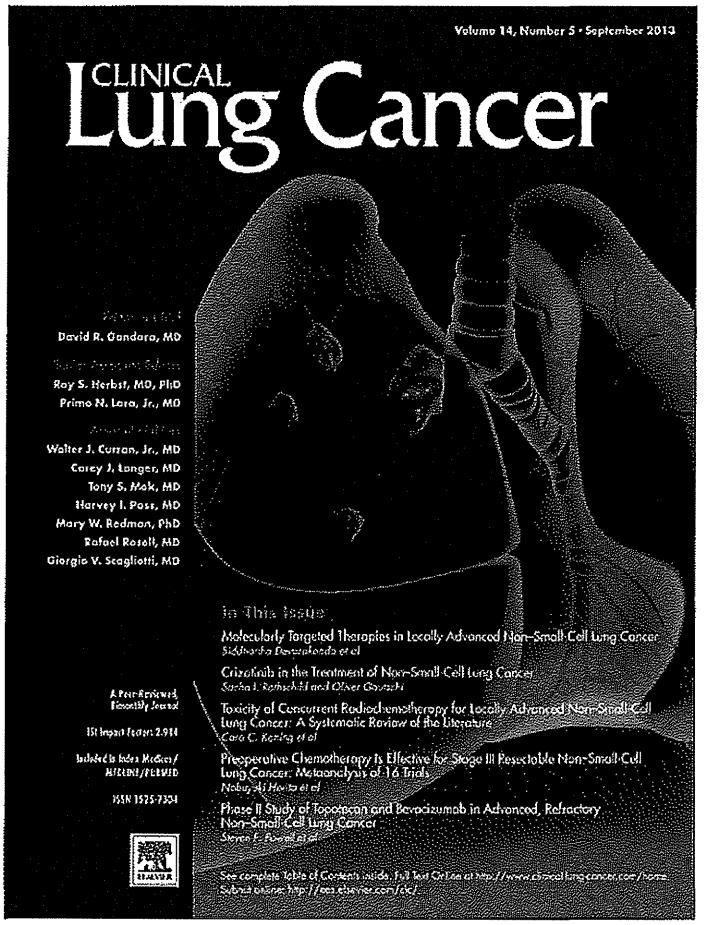

Current Trial Report

Rationale and Design of the Japan Molecular Epidemiology for Lung Cancer Study

Tomoya Kawaguchi,[1] Masahiko Ando,[2] Norimasa Ito,[3] Shun-Ichi Isa,[4] Akihiro Tamiya,[1] Shigeki Shimizu,[5] Hideo Saka,[6] Akihito Kubo,[7] Yasuhiro Koh,[8] Akihide Matsumura[3]

Abstract

We present the rationale for the Japan Molecular Epidemiology for Lung Cancer study designed to elucidate molecular mechanisms of carcinogenesis in smokers and never-smokers with non–small-cell lung cancer. This prospective, ongoing, multicenter study is being conducted nationwide in Japan. Although there is no doubt that active smoking is the major cause of lung cancer, the contribution of other possible factors, including environmental tobacco or wood smoke, human papilloma virus, radon, occupational exposures, and genetic susceptibility, is highly likely, based on studies of never-smokers with non–small-cell lung cancer. Because of the predominance of women in the never-smoker subgroup, the role of female hormones in lung cancer development has also been considered. We hypothesize that driver mutations, which are critical for the development of lung cancer, are triggered by the environmental factors with or without the influence of the hormone. The SWOG-led intergroup molecular epidemiology study S0424 was conducted to focus on these issues by using a detailed questionnaire and specimen collection in statistically significant cohorts of smokers and never-smokers from both sexes. The Japan Molecular Epidemiology for Lung Cancer study follows and extends the S0424 molecular epidemiology concept in principle by using a similar approach that will facilitate future comparisons between the studies but with a greater focus on more recently defined driver mutations and broad genomic sequencing.

Clinical Lung Cancer, Vol. 14, No. 5, 596-600
Keywords: Driver mutations, Molecular epidemiology, Never-smokers, Non–small-cell lung cancer, Smokers

Introduction

Lung cancer is a leading cause of cancer-related morbidity and mortality in the world. Although the disease is predominantly caused by tobacco smoke, approximately 25% of all lung cancers worldwide are not attributable to this etiology. In fact, approximately 30% of Japanese patients with non–small-cell lung cancer (NSCLC) are never-smokers, as observed in a study that consisted of more than 20,000 patients.[1] Lung cancer in never-smokers differs significantly from that of smokers in clinical characteristics and in the distribution of oncogenic abnormalities, and it has been suggested to be a distinct disease.[2]

Although several possible explanations have been proposed, the cause of lung cancer in never-smokers remains unclear. Explanations include environmental tobacco smoke (ETS) exposure,[3] radon,[4] wood smoke,[5] occupational exposure,[6] oncogenic virus,[7,8] genetic change,[9] and sex hormone.[10,11] A Japan Public Health Center–based prospective study showed that, in Japan, second-hand smoke exposure is clearly related to the development of lung adenocarcinoma in never-smokers.[3] The study identified a statistically significant dose-response relationship between the quantity and the intensity of husbands' smoking and their wives' incidence of lung cancer. Our previous study with a detailed questionnaire in a prospective way enhances this finding that the development of epidermal growth factor receptor (*EGFR*) mutations is significantly associated with the dose of ETS exposure in never-smokers.[12] However, there are con-

[1]Department of Internal Medicine, National Hospital Organization, Kinki-chuo Chest Medical Center, Osaka, Japan
[2]Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan
[3]Department of Surgery, National Hospital Organization, Kinki-chuo Chest Medical Center, Osaka, Japan
[4]Clinical Research Center, National Hospital Organization, Kinki-chuo Chest Medical Center, Osaka, Japan
[5]Department of Pathology, National Hospital Organization, Kinki-chuo Chest Medical Center, Osaka, Japan
[6]Department of Respiratory Medicine, National Hospital Organization, Nagoya Medical Center, Nagoya, Japan
[7]Division of Respiratory Medicine and Allergology, Aichi Medical University School of Medicine, Nagakute, Japan
[8]Division of Drug Discovery and Development, Shizuoka Cancer Center Research Institute, Sunto-gun, Japan

Submitted: Nov 22, 2012; Revised: Feb 26, 2013; Accepted: Mar 26, 2013; Epub: May 17, 2013

Address for correspondence: Tomoya Kawaguchi, MD, Department of Internal Medicine, National Hospital, Organization Kinki-chuo Chest Medical Center, Sakai, Osaka 591–8555, Japan
E-mail contact: t-kawaguchi@kch.hosp.go.jp

1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.cllc.2013.03.001

flicting data published on the relationship between ETS and *EGFR* mutations in never-smokers with NSCLC. A study from Korea showed opposite results, in which the development of the mutation was inversely proportional to the ETS[13]; although, in the United States, there was no association between them.[14] A study with a well-designed and standardized questionnaire in a larger sample size is required to conclude this issue.

An oncogenic role for the HPV has been widely investigated in NSCLC.[7] Although all the published reports were retrospective analyses with potentially significant limitations and bias, the systematic review nevertheless suggested that the development of lung cancer in Asia can be attributed to some extent to HPV. Moreover, a different detection rate was observed geographically even within east Asia, with a higher rate in the southern area than in the northern regions. There is a substantial need to confirm these findings by using a standardized HPV detection methodology in a prospective study in Japanese patients.

The association between sex and lung cancer carcinogenesis is also an important consideration. Although studies provide conflicting results on the strength of this association, it has been postulated that women are more vulnerable to tobacco smoke–associated carcinogens than men. The large SWOG study S0424 was originally designed to address this issue by using a detailed questionnaire and NSCLC tissue specimens from smoker and never-smoker men and women with newly diagnosed stage I, stage II, or stage III NSCLC,[15] in which polycyclic aromatic hydrocarbons and aromatic amines of DNA adducts are measured to quantitate levels of DNA damage stratified by sex and the smoking status. Cigarette smoke contains a large number of carcinogens, and polycyclic aromatic hydrocarbons and aromatic amines are among the most important contributors to the carcinogenic process. The Japan Molecular Epidemiology for lung cancer (JME) study follows and extends the concept of S0424 by using a similar approach that will allow for direct comparison of data in the future.

Sex hormones, including estrogen and progesterone, have been suggested to play an important role in lung carcinogenesis. Results of epidemiologic studies showed that women were predominant in number in the never-smoking subpopulation. Further, results of large randomized studies suggest that estrogen plus progestin therapy is associated with an increased risk of lung cancer. The prospective Vitamins and Lifestyle Study followed a cohort of more than 36,000 peri- and postmenopausal women during 6 years of follow-up.[16] After adjusting for smoking and other confounding factors, the incidence of lung cancer was increased for those who used estrogen plus progestin. The risk was proportional to the duration of hormone exposure (hazard ratio 1.48 [95% CI, 1.03-2.12] for those with ≥10 years of exposure to estrogen plus progestin).

In terms of biologic function, estrogen receptors (ER) are expressed in diverse normal and neoplastic tissues, and mediate growth and maturation of normal tissue. A number of studies have noted expression of ERs in a large portion of lung tumors. In a couple of studies, the development of *EGFR* mutations was significantly associated with expression of ER β in NSCLC surgical specimens.[10,11] There have been no studies that systematically evaluated ER expression in lung cancer and its relationship with genetic mutations or environmental and reproductive risk factors.

Identification of driver mutations in NSCLC has been instrumental in improving treatment strategies. *ALK* (anaplastic lymphoma kinase) gene translocations have been demonstrated to be critical targets and biomarkers for crizotinib efficacy,[17] similar to *EGFR* mutations for gefitinib and erlotinib, and the discovery of other mutations for treatment is ongoing. The Lung Cancer Mutational Consortium in the United States[18] and the Lungscape project in the European Union[19] are currently exploring new molecular targets for treatment in lung cancer. Powerful tools for genome-wide characterization have been developed, including next-generation sequencing, which enables comprehensive examination of somatic mutations associated with carcinogenesis. The Cancer Genome Atlas is an ongoing global project that uses this technology to distill essential driver abnormalities from the background noise.[20] A focus of the JME study is to explore new driver mutations by using advanced technologies and approaches now available with regard to sex of the patient and tobacco smoke exposure. The association between oncogenic abnormality profiles and drug sensitivity and prognosis will also be examined.

In addition, the JME study is designed to investigate the relationship between ethnicity and NSCLC carcinogenesis. It is clear that NSCLCs are different in tumor biology between Caucasian and Asian patients. Gandara et al[21] showed that there was a significant difference in survival and toxicities between the US and the Japanese patients treated with carboplatin and paclitaxel in a "common arm" trial, in which the study design, eligibility criteria, and staging were similar. The median overall survival in the metastatic disease was 12 and 14 months for Japanese patients vs. 9 months for US patients ($P = .0006$).[21] As for *EGFR* mutations, the frequencies appear to be highly distinct; the high detection rate in Asia was reported consistently across publications. Different influences of smoking status on the development of NSCLC also was observed between the United States and Japan in population-based prospective studies. In a comparison of the Japanese cohort with US Cancer Prevention Study II during the same period,[22] Japanese never-smokers had an increased risk of lung cancer, whereas Japanese current smokers were at a lower risk of the cancer compared with those in the United States. To elucidate the mechanistic contributions of ethnic differences, there is a need to collaborate in comprehensive and global approaches for examining development of NSCLC as well as the clinical behavior and outcome.

Objectives

The primary objective of this study is to assess surgical lung specimens from patients with stage I, stage II, stage IIIA, or stage IIIB NSCLC for driver mutations, expression of HER2 and ER α and ER β, the presence of smoking-associated DNA adducts, and evidence of HPV, and to explore new molecular markers by using next-generation sequencing. By using information collected before surgery on patient demographics, smoking history and occupational exposures, carcinogenic mechanisms will be elucidated in never-smokers and ever-smokers. Secondary objectives are to examine whether the relapse rate, disease-free survival, and overall survival time differ among the patients with different mutational

spectrums, and whether mutational profiles differ between Japanese and Caucasian populations.

Patients and Methods

Eligible patients are those with pathologically proven NSCLC with stage I and II, IIIA, or IIIB disease[23] who underwent surgery with a curative intent (Figure 1). Patients with prior chemotherapy and/or radiotherapy are excluded, as are patients with other prior malignancies except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Patients are stratified according to smoking status. Never-smokers are defined as those who smoked fewer than 100 cigarettes during their lifetime, and ever-smoker who smoked 100 or more cigarettes during their lifetime.

Patients are required to complete the questionnaire before surgery for detailed assessment of the following: exposure to active and passive smoke, occupational exposures, reproductive and hormonal risk factors, weight loss, family history of cancer, medication use, and diet and exercise. DNA is extracted from all formalin-fixed paraffin-embedded surgical tissues. *EGFR* and *KRAS* (v-Ki-ras2 Kirsten rat sarcoma) mutations are examined by using real-time polymerase chain reaction and *ALK* by immunohistochemical staining and fluorescence in situ hybridization. HPV genotyping is performed by using a polymerase chain reaction–based microarray system for detection of 23 HPV types, including high-risk (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and low-risk or risk-unknown types (HPV types 6, 11, 30, 34, 40, 42, 53, 54, 61, and 66). In addition, multiplexed targeted deep sequencing is applied to the tumors, including 48 cancer-associated genes, such as *ABL1, AKT1, CSF1R, CTNNB1, IDH1, MET, MLH1, PIC3CA, RET, STK11,* and *TP53*.

Surgical samples are examined for DNA adducts levels, and polycyclic aromatic hydrocarbons and/or aromatic amines–induced DNA damage is assessed by immunohistochemical staining and immunofluorescence. ER α and ER β are assessed by immunohistochemistry. Patients will be followed up annually for up to 4 years to capture relapse rate, disease-free survival, and overall survival time. Whether mutational profiles differ between Japanese and Americans will be determined after adjusting for sex, smoking status, and other clinical backgrounds.

Statistical Consideration

Sample size in this study is 900 patients, which consists of 450 ever-smokers and 450 never-smokers, which was calculated to ensure >80% power for testing all individual hypotheses at the 2-sided .05 significance level. Based on the review article including the published data,[24] the assumed proportion of patients with *EGFR* mutation is expected to be approximately 7% and 45% in smokers and never-smokers, respectively. Mutation of *KRAS* is expected to be 30% to 43% in smokers and 0% to 7% in never-smokers. When several examples are given to detect differences of 30% to 50% in mutation-positive frequency between smokers and never-smokers, the power is >90% in most cases. Less common driver mutations are also considered and calculated based on published data[17]; the assumed proportion of patients with *ALK* fusion is expected to be approximately 3.5% and 9.9% in smokers and never-smokers, respectively. The power is >90% in most cases to detect differences of 5% to 7% in fusion-positive frequency between the 2 groups.

According to our study in never-smokers,[12] more *EGFR* mutations were observed in those who had longer ETS exposure. When the length of ETS is divided by the median of the value, if the *EGFR* detection rate differs by more than 15% between the 2 groups overall, then the power is >90% in most cases.

The meta-analysis on HPV and lung cancer showed that, when using polymerase chain reaction, there were 22% of cases (95% CI, 18%-27%) possibly associated with the virus.[8] The presence of HPV is expected to be observed at least in approximately 160 patients in smokers and never-smokers, and the geographic distribution is also examined.

Based on our previous study, which included approximately 20,000 Japanese patients,[1] it is assumed that 350 female never-smokers, 100 male never-smokers, 120 female ever-smokers and 330 male ever-smokers will be accrued in this study. A possible fluctuation in accrual on sex is expected to be with a range of ±20%. If the detection rate of *EGFR* mutation differs by more than 15% between male and female subjects, then the power is >90% in most cases overall and >80% in most cases within smokers and never-smokers.

The prognostic value of each unique *EGFR* and *KRAS* mutation, along with other abnormalities, will initially be assessed by using multivariable proportional hazards regression when adjusting for strata. Relationships will be graphically displayed for each prognostic group by using Kaplan-Meier curves. The classification and regression tree method will be used to identify prognostic risk groups based on these measures of the mutations combined with other patient demographic and correlative data.

Conclusion

The JME study is a prospective project sponsored by an independent administrative agency in Japan to use advanced molecular technologies to improve our understanding of the underlying biology of NSCLC in Japanese patients nationwide. The primary focus of this study is on the relationships among tumor carcinogenesis; patterns of biomarkers, including driver mutations; and detailed demographic information. This study is currently ongoing, and successful accrual to date supports the feasibility of the study design. The outcomes of the JME study will have clinical implication with respect to establishing a model for lung cancer carcinogenesis and will provide a wealth of information on driver mutations to better understand the tumor carcinogenic process and to improve therapeutic options for patients with NSCLC.

Acknowledgments

We thank Drs David Gandara and Philip Mack of the University of California Davis Comprehensive Cancer Center for their critical review and Ms Naoko Akeda for her excellent technical assistance. This study is conducted as a project of the Japanese National Hospital Organization Multi-Center Clinical Research for Evidence-based Medicine. This study was supported by a Grant-in-Aid for Japanese National Hospital Organization Multi-Center Clinical Research for evidence-based medicine, Japan.

Figure 1 Scheme of the Japan Molecular Epidemiology for Lung Cancer