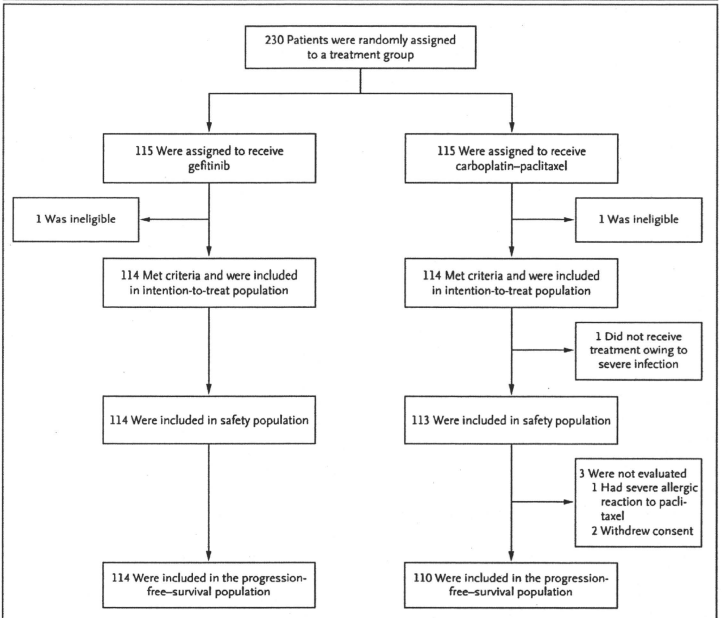


Figure 1. Randomization and Follow-up of the Study Patients, According to Treatment Group.

At the data cutoff point (early December 2009), the median follow-up period was 527 days (>17 months; range, 30 to 1261). The median duration of gefitinib treatment was 308 days (range, 14 to 1219); the median number of 3-week cycles of chemotherapy was 4 (range, 1 to 7). Three patients in the gefitinib group and 11 patients in the chemotherapy group received second-line treatment before they had RECIST-defined disease progression. The data on progression-free survival for these patients were censored at the time of the last CT evaluation at which they did not yet have evidence of disease progression. Demographic and disease characteristics at baseline were well balanced between the two groups (Table 1).

EFFICACY

The interim analysis performed in May 2009 showed that progression-free survival was significantly longer in the gefitinib group than in the chemotherapy group (median, 10.4 months vs. 5.5 months; hazard ratio for death or disease progression with gefitinib, 0.36; 95% confidence interval [CI], 0.25 to 0.51; P<0.001) (Fig. 1 in the Supplementary Appendix). A significant difference was again observed in the final analysis, performed in December 2009 (median progression-free survival, 10.8 months with gefitinib vs. 5.4 months with chemotherapy; hazard ratio, 0.30; 95% CI, 0.22 to 0.41; P<0.001) (Fig. 2A). The 1-year and 2-year rates of progression-free survival were 42.1% and 8.4%, respectively, in the gefitinib group and 3.2% and 0%, respectively, in the chemotherapy group. Subgroup analyses showed that women had significantly longer progression-free survival than men (median, 6.5 vs. 6.0 months; hazard ratio for death or disease progression, 0.68; 95% CI, 0.51 to 0.92; P=0.01). The objective response rate was significantly higher in the gefitinib group than the chemotherapy group (73.7% vs. 30.7%,

Table 1. Baseline Characteristics of the Intention-to-Treat Population, According to Treatment Group.*

Characteristic	Gefitinib (N=114)	Carboplatin–Paclitaxel (N=114)
Sex — no. (%)		
Male	42 (36.8)	41 (36.0)
Female	72 (63.2)	73 (64.0)
Age — yr		
Mean	63.9±7.7	62.6±8.9
Range	43–75	35–75
Smoking status — no. (%)		
Never smoked	75 (65.8)	66 (57.9)
Previous or current smoker	39 (34.2)	48 (42.1)
ECOG performance status score — no. (%)		
0	54 (47.4)	57 (50.0)
1	59 (51.8)	55 (48.2)
2	1 (0.9)	2 (1.8)
Histologic diagnosis — no. (%)		
Adenocarcinoma	103 (90.4)	110 (96.5)
Large-cell carcinoma	1 (0.9)	0
Adenosquamous carcinoma	2 (1.8)	1 (0.9)
Squamous-cell carcinoma	3 (2.6)	2 (1.8)
Other	5 (4.4)	1 (0.9)
Clinical stage — no. (%)		
IIIB	15 (13.2)	21 (18.4)
IV	88 (77.2)	84 (73.7)
Postoperative relapse	11 (9.6)	9 (7.9)
Type of EGFR mutation — no. (%)		
Exon 19 deletion	58 (50.9)	59 (51.8)
L858R	49 (43.0)	48 (42.1)
Other	7 (6.1)	7 (6.1)

* Plus–minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group.

P<0.001) (Table 2). The median progression-free survival and response rate did not differ significantly between patients with the EGFR mutation consisting of an exon 19 deletion (11.5 months and 82.8%) and those with the L858R point mutation (in which leucine at amino acid 858 is replaced by arginine) (10.8 months and 67.3%) (Fig. 2B).

The overall survival did not differ significantly between the two treatment groups. The median survival time and the 2-year survival rate were 30.5 months and 61.4% for the gefitinib group, as compared with 23.6 months and 46.7%, respectively, for the carboplatin–paclitaxel group (P=0.31) (Fig. 2C). Neither sex nor clinical stage had a significant effect on overall survival. The time to an ECOG performance status score of 3 or more did not differ significantly between the two groups.

SAFETY

All patients who had received at least one dose of a study drug were included in the safety analysis. The most common adverse events in the gefitinib group were rash and elevated levels of aspartate aminotransferase or alanine aminotransferase, and in the chemotherapy group, appetite loss, neutropenia, anemia, and sensory neuropathy (Table 3, and Table 3 in the Supplementary Appendix). Interstitial lung disease was reported in six patients (5.3%) in the gefitinib group; three cases were severe, and one of the three was fatal. One grade 4 seizure in the gefitinib group and one grade 4 cerebral infarction and one grade 4 bowel obstruction in the chemotherapy group were observed. The incidence of severe toxic effects (NCI-CTC grade ≥3) was significantly higher in the chemotherapy group than in the gefitinib group (71.7% vs. 41.2%, P<0.001).

TREATMENT AFTER PROTOCOL DISCONTINUATION

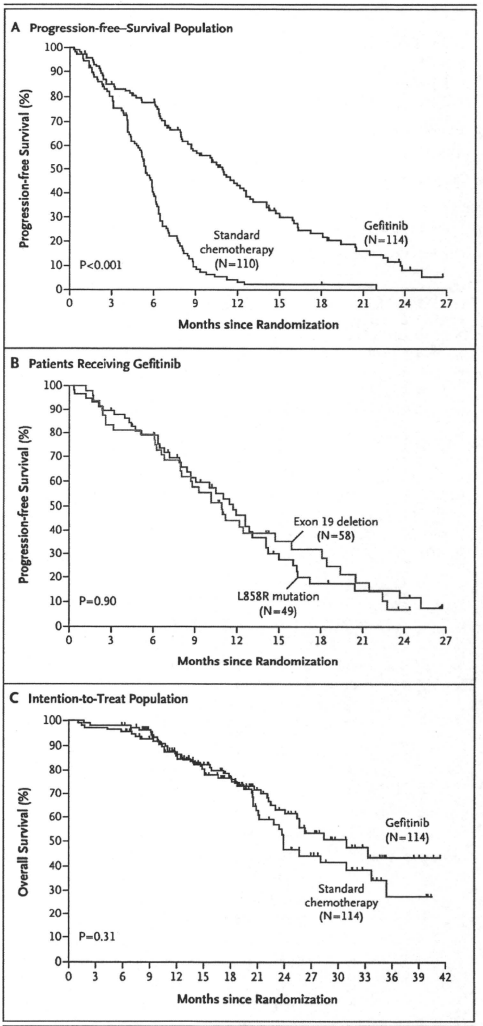
Data on treatment given after the study protocol was discontinued were collected retrospectively. Though any treatment was permitted, the protocol recommended that the crossover regimen be used as second-line treatment. As of the data cutoff point, 37 patients in the gefitinib group had continued their first-line gefitinib therapy. Among the remaining 77 patients in the gefitinb group who had stopped receiving gefitinib, 52 (67.5%) were receiving carboplatin–paclitaxel as second-line treatment, with a response rate of 28.8%. Sixteen other patients in the gefitinib group were receiving other therapies such as carboplatin–gemcitabine. Among the 112 patients who had completed first-line carboplatin–paclitaxel, 106 patients (94.6%) received second-line gefitinib; 58.5% of these patients had a response.

DISCUSSION

Previous phase 2 studies have suggested that EGFR tyrosine kinase inhibitors are highly effective against mutated-EGFR non–small-cell lung cancer. The current phase 3, prospective, randomized study showed that the use of gefitinib results in progression-free survival that is twice as long

Figure 2. Progression-free Survival and Overall Survival among the Study Patients.

Kaplan–Meier curves for progression-free survival are shown for the progression-free–survival population (Panel A) and for the 107 patients in the gefitinib group with either of the two most common types of epidermal growth factor receptor (EGFR) mutation (Panel B). Kaplan–Meier curves for overall survival in the intention-to-treat population are shown in Panel C. In Panels B and C, tick marks indicate patients for whom data were censored at the data cutoff point (early December 2009).



as that obtained with the use of carboplatin–paclitaxel in patients with mutated-EGFR non–small-cell lung cancer, with a tolerable toxicity profile, including less hematologic toxicity and neurotoxicity than is seen with chemotherapy.

The IPASS, which was conducted in Asia, compared gefitinib with carboplatin–paclitaxel as the first-line treatment for advanced non–small-cell lung cancer in patients selected on the basis of clinical characteristics that included a history of no smoking or light smoking as well as histologic evidence of adenocarcinoma.[7] Although IPASS showed the overall superiority of gefitinib (rate of 1-year progression-free survival, 24.9%, vs. 6.7% with chemotherapy; hazard ratio for death or disease progression, 0.74; P<0.001), the most impressive result emerged from subgroup analysis: as compared with chemotherapy, gefitinib was effective in patients with mutant EGFR (hazard ratio for death or disease progression, 0.48) but was ineffective in those with wild-type EGFR (hazard ratio, 2.85). This finding suggested that the presence of EGFR mutations is the best criterion for selection of patients who benefit from gefitinib, an idea that is validated by the present study.[20] Recently, another Japanese phase 3 study (WJTOG3405; University Hospital Medical Information Network Clinical Trials Registry [UMIN-CTR] number, UMIN000000539) compared gefitinib to cisplatin–docetaxel as the first-line treatment for advanced non–small-cell lung cancer with EGFR mutations.[21] Although this study also showed the superiority of gefitinib over standard chemotherapy with respect to progression-free survival, the magnitude of the benefit was somewhat smaller than in our study, possibly because of differences in the characteristics of the patients (since 41% of patients in WJTOG3405 had had surgery, vs. only 9% in our study) and the duration of follow-up (median, 81 days in WJTOG3405 vs. 527 days in our study).

The standard end point of phase 3 trials of treatments for advanced non–small-cell lung cancer has been overall survival. However, when our trial was begun in 2006, we had data only on

Table 2. Response to Treatment in the Intention-to-Treat Population, According to Treatment Group.*

Response	Gefitinib (N=114)	Carboplatin–Paclitaxel (N=114)
	number of patients (percent)	
Complete response	5 (4.4)	0
Partial response	79 (69.3)	35 (30.7)
Complete or partial response†	84 (73.7)	35 (30.7)
Stable disease	18 (15.8)	56 (49.1)
Progressive disease	11 (9.6)	16 (14.0)
Response that could not be evaluated	1 (0.9)	7 (6.1)

* All responses differed significantly between the two groups (P<0.001 by Fisher's exact test).

† The percentage of patients in whom there was either a complete or a partial response was considered to be the rate of objective response.

progression-free survival from our phase 2 studies in patients with non–small-cell lung cancer and EGFR mutations. The data on overall survival first became available in 2008, when the combined analysis of Japanese phase 2 studies (Iressa — Combined Analysis of Mutation Positives [I-CAMP]) and the subgroup analyses of IPASS were reported.[7,22] We thus planned to have progression-free survival as the primary end point in the current study, because it allowed us to calculate the statistical power of the study.

Several studies have suggested that the EGFR copy number may be a better predictive biomarker for the efficacy of EGFR tyrosine kinase inhibitors than the presence of an EGFR mutation.[23] However, its predictive capacity has been reported only in placebo-controlled trials (Iressa Survival Evaluation in Lung Cancer [ISEL][24] and the BR.21 study[23]). Moreover, the subgroup analysis in IPASS showed that longer progression-free survival was significantly associated with sensitive EGFR mutations but not with a high EGFR copy number. We therefore believe that evaluation of the copy number is not necessary when an EGFR mutation test is available. In the current study, EGFR mutations were detected with the use of the PNA-LNA PCR clamp method, the usefulness of which has been validated.[15,16] With this method, EGFR mutations can be detected from small cytologic specimens, such as those from bronchial washings, pleural effusions, and sputum collection, which are frequently used for the diagnosis of advanced non–small-cell lung cancer. The results of the analyses are obtained within several days, so the treatment is usually not delayed. The PNA-LNA PCR clamp approach is readily available and is covered by health insurance in Japan.

The best timing of treatment with an EGFR tyrosine kinase inhibitor for patients with EGFR mutations remains undetermined. A recent study showed that overall survival did not differ significantly between first-line and second-line treatments with erlotinib.[25] Overall survival is considered to be influenced by the second-line or later treatment. In the current study, 95% of the patients in whom first-line carboplatin–paclitaxel failed crossed over to gefitinib therapy. Such a high crossover rate has not been reported in previous studies of EGFR tyrosine kinase inhibitors. For example, in IPASS, only 39% of patients in the first-line chemotherapy group later received an EGFR-tyrosine kinase inhibitor. Considering that in our study the median overall survival in the gefitinib group was 7 months longer than that in the chemotherapy group (30.5 months vs. 23.6 months), in which virtually all patients were given gefitinib as the second-line treatment, and that the rate of response to gefitinib was slightly worse in the second-line setting than in the first-line setting (58.5% vs. 73.7%), first-line gefitinib may be more effective than gefitinib as second-line or later therapy. This idea needs to be tested in studies with large samples or in a meta-analysis.

We believe that the prolonged progression-free survival provided by the use of first-line gefitinib is valuable for patients with advanced non–small-cell lung cancer, who have a poor prognosis. If gefitinib is administered as second-line or third-line treatment, patients may miss the opportunity to receive treatment with gefitinib because of rapidly progressive disease during or after first-line treatment. We believe that the current study, in combination with our previous study of patients with mutated-EGFR non–small-cell lung cancer and poor performance status,[26] establishes the clinical benefit of an EGFR tyrosine kinase inhibitor as first-line treatment in patients with non–small-cell lung cancer and sensitive EGFR mutations.

Predictable toxicity profiles were observed with gefitinib and with carboplatin–paclitaxel in the current study. Diarrhea and rash were seen more often in the gefitinib group, whereas hematologic and neurologic toxic effects were more common in the chemotherapy group. Gefitinib appears to

Table 3. Common Toxic Effects in the Safety Population, According to Treatment Group.*

Toxic Effect	Gefitinib (N=114)					Carboplatin–Paclitaxel (N=113)					P Value for Grade ≥3
	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3	
	no. of patients				*no. (%)*	*no. of patients*				*no. (%)*	
Diarrhea	32	6	1	0	1 (0.9)	7	0	0	0	0	<0.001
Appetite loss	7	4	6	0	6 (5.3)	39	18	7	0	7 (6.2)	<0.001
Fatigue	8	1	3	0	3 (2.6)	19	11	1	0	1 (0.9)	0.002
Rash	38	37	6	0	6 (5.3)	8	14	3	0	3 (2.7)	<0.001
Neuropathy (sensory)	0	1	0	0	0	28	27	7	0	7 (6.2)	<0.001
Arthralgia	1	2	1	0	1 (0.9)	25	21	8	0	8 (7.1)	<0.001
Pneumonitis	3	0	2	1†	3 (2.6)	0	0	0	0	0	0.02
Aminotransferase elevation	20	13	29	1	30 (26.3)	31	5	0	1	1 (0.9)	<0.001
Neutropenia	5	1	0	1	1 (0.9)	4	9	37	37	74 (65.5)	<0.001
Anemia	19	2	0	0	0	35	32	6	0	6 (5.3)	<0.001
Thrombocytopenia	8	0	0	0	0	25	3	3	1	4 (3.5)	<0.001
Any	17	44	43	4†	47 (41.2)	4	25	41	40	81 (71.7)	<0.001

* Toxic-effect grades are based on the National Cancer Institute Common Terminology Criteria (version 3.0).
† One patient counted here had a grade 5 toxic effect.

be less toxic than carboplatin–paclitaxel. The only exception was interstitial lung disease; there were three cases of severe interstitial lung disease (≥grade 3) in the gefitinib group and none in the chemotherapy group; one of the cases was fatal. The patient who died was a woman who had no history of smoking and thus had a relatively low risk of interstitial lung disease. Gefitinib sometimes causes diffuse alveolar or interstitial damage, especially during the first 3 months of treatment.[27] The estimated incidence of interstitial lung disease is low in many countries (e.g., 0.3% in United States)[28] but is relatively high (4 to 6%) in Japan.[29,30] Every patient treated with an EGFR tyrosine kinase inhibitor should be carefully monitored for this toxic effect.

In conclusion, the efficacy of first-line gefitinib was superior to that of standard chemotherapy, with acceptable toxicity, in patients with advanced non–small-cell lung cancer harboring sensitive EGFR mutations. Selection of patients on the basis of EGFR-mutation status is strongly recommended.

Supported by grants-in-aid from the Japan Society for Promotion of Science and the Japanese Foundation for the Multidisciplinary Treatment of Cancer and a grant from the Tokyo Cooperative Oncology Group.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all our patients and their families, as well as all the site investigators; and Dr. Koichi Yamazaki (deceased), former associate professor of the First Department of Medicine, Hokkaido University School of Medicine.

APPENDIX

The authors' affiliations are as follows: Miyagi Cancer Center, Miyagi (M.M.); Tohoku University Hospital (A.I., T.N.); Sendai Kousei Hospital (S.S.); and Tohoku University Graduate School of Medicine (T.N.) — all in Sendai; Saitama Medical University International Medical Center (K.K.) and Saitama Medical University (H.M., T.T., K.H.) — both in Saitama; Hokkaido University School of Medicine (S. Oizumi), Kokka-komuin Kyosai-kumiai Rengokai Sapporo Medical Center (H.I.), National Hospital Organization Hokkaido Cancer Center (M.H.), Hokkaido University Graduate School of Medicine (I.K.), and Hokkaido Social Insurance Hospital (T.H.) — all in Sapporo; Nippon Medical School (A.G.) and Anti-Tuberculosis Association Fukujuji Hospital (K.Y.) — both in Tokyo; Niigata University Medical and Dental Hospital, Niigata (H.Y.); National Hospital Organization Dohoku National Hospital, Asahikawa (Y.F.); Kesennuma City Hospital, Miyagi (S. Okinaga); Iwate Prefectural Central Hospital, Morioka (H.H.); Kanagawa Cardiovascular and Respiratory Center (T.O.) and Yokohama City University Medical Center (S.M.) — both in Yokohama; Tsuboi Cancer Center Hospital, Koriyama (M.A.); and Graduate School of Medicine, Hirosaki University, Hirosaki (Y.S.) — all in Japan.

Contributing members of the North-East Japan Study Group were as follows: **Steering Committee** — K. Kobayashi, A. Inoue, K. Yamazaki, S. Oizumi, H. Isobe, Y. Saijo, K. Hagiwara, A. Gemma, T. Nukiwa; **Advisers to Steering Committee** — S. Kudoh, M. Kanazawa; **Independent Data and Safety Monitoring Committee** — K. Nagao, Y. Nakai, M. Shibuya; **Study Site Investigators** —

K. Akie, N. Chonabayashi, Y. Hasegawa, K. Hayashibara, M. Hino, T. Hino, K. Ikebuchi, Y. Ishii, N. Kaneko, Y. Kimura, H. Koba, T. Kojima, S. Kosaihira, N. Koyama, H. Miki, Y. Minegishi, N. Morikawa, G. Moriyama, Y. Murayama, M. Nagashima, K. Niizuma, H. Nitanai, S. Ogura, Y. Okamoto, Y. Osaki, H. Sakai, H. Sugita, T. Suzuki, J. Tanaka, H. Tokunaga, T. Tsukamoto, K. Uematsu, K. Usui, K. Yasuda.

REFERENCES

1. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non–small-cell lung cancer. N Engl J Med 2002;346:92-8.
2. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007;18:317-23.
3. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (the IDEAL 1 Trial). J Clin Oncol 2003;21:2237-46. [Erratum, J Clin Oncol 2004;22:4811.]
4. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 2003;290:2149-58.
5. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;372: 1809-18.
6. Maruyama R, Nishiwaki Y, Tamura T, et al. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. J Clin Oncol 2008;26:4244-52.
7. Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
8. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
9. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500.
10. Mitsudomi T, Kosaka T, Endoh H, et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. J Clin Oncol 2005;23: 2513-20.
11. Toyooka S, Takano T, Kosaka T, et al. Epidermal growth factor receptor mutation, but not sex and smoking, is independently associated with favorable prognosis of gefitinib-treated patients with lung adenocarcinoma. Cancer Sci 2008;99:303-8.
12. Inoue A, Suzuki T, Fukuhara T, et al. Prospective phase II study of gefitinib for chemotherapy-naive patients with advanced non-small-cell lung cancer with epidermal growth factor receptor gene mutations. J Clin Oncol 2006;24:3340-6.
13. Asahina H, Yamazaki K, Kinoshita I, et al. A phase II trial of gefitinib as first-line therapy for advanced non-small cell lung cancer with epidermal growth factor receptor mutations. Br J Cancer 2006;95: 998-1004.
14. Sutani A, Nagai Y, Udagawa K, et al. Gefitinib for non-small-cell lung cancer patients with epidermal growth factor receptor gene mutations screened by peptide nucleic acid-locked nucleic acid PCR clamp. Br J Cancer 2006;95:1483-9.
15. Nagai Y, Miyazawa H, Huqun, et al. Genetic heterogeneity of the epidermal growth factor receptor in non-small cell lung cancer cell lines revealed by a rapid and sensitive detection system, the peptide nucleic acid-locked nucleic acid PCR clamp. Cancer Res 2005;65:7276-82.
16. Tanaka T, Matsuoka M, Sutani A, et al. Frequency of and variables associated with the EGFR mutation and its subtypes. Int J Cancer 2010;126:651-5.
17. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205-16.
18. Bell DW, Lynch TJ, Haserlat SM, et al. Epidermal growth factor receptor mutations and gene amplification in non–small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials. J Clin Oncol 2005;23:8081-92.
19. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
20. Kobayashi K, Inoue A, Maemondo M, et al. First-line gefitinib versus first-line chemotherapy by carboplatin (CBDCA) plus paclitaxel (TXL) in non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations: a phase III study (002) by North East Japan Gefitinib Study Group. J Clin Oncol 2009;27:Suppl:411s. abstract.
21. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-8.
22. Morita S, Okamoto I, Kobayashi K, et al. Combined survival analysis of prospective clinical trials of gefitinib for non-small cell lung cancer with EGFR mutations. Clin Cancer Res 2009;15:4493-8.
23. Shepherd FA, Pereira JR, Ciuleanu T, et al. Erlotinib in previously treated non–small-cell lung cancer. N Engl J Med 2005;353:123-32.
24. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005;366:1527-37.
25. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361:958-67.
26. Inoue A, Kobayashi K, Usui K, et al. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. J Clin Oncol 2009;27:1394-400. [Erratum, J Clin Oncol 2009;27:3071.]
27. Inoue A, Saijo Y, Maemondo M, et al. Severe acute interstitial pneumonia and gefitinib. Lancet 2003;361:137-9.
28. Cohen MH, Williams GA, Sridhara R, Chen G, Pazdur R. FDA drug approval summary: gefitinib (ZD1839) (Iressa) tablets. Oncologist 2003;8:303-6.
29. Ando M, Okamoto I, Yamamoto N, et al. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. J Clin Oncol 2006; 24:2549-56.
30. Kudoh S, Kato H, Nishiwaki Y, et al. Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. Am J Respir Crit Care Med 2008;177:1348-57.

Annals of Oncology Advance Access published October 8, 2009

original article

Annals of Oncology
doi:10.1093/annonc/mdp401

Randomized phase II trial of weekly paclitaxel combined with carboplatin versus standard paclitaxel combined with carboplatin for elderly patients with advanced non-small-cell lung cancer

T. Sakakibara[1]*, A. Inoue[1], S. Sugawara[2], M. Maemondo[3], T. Ishida[4], K. Usui[5], T. Abe[6], M. Kanbe[7], H. Watanabe[8], Y. Saijo[9] & T. Nukiwa[1]

[1]*Department of Respiratory Medicine, Tohoku University Hospital;* [2]*Department of Respiratory Medicine, Sendai Kousei Hospital, Sendai;* [3]*Department of Respiratory Medicine, Miyagi Cancer Center, Natori;* [4]*Department of Respiratory Medicine, Fukushima Medical University Hospital, Fukushima;* [5]*Department of Respiratory Medicine, Kanto Medical Center NTT EC, Shinagawa-ku, Tokyo;* [6]*Department of Respiratory Medicine, Tohoku Kouseinenkin Hospital, Sendai;* [7]*Department of Respiratory Medicine, Senseki Hospital, Higashimatsushima, Yamoto;* [8]*Department of Respiratory Medicine, Saka General Hospital, Shiogama and* [9]*Department of Medical Oncology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan*

Received 1 June 2009; revised 8 July 2009; accepted 9 July 2009

Background: The optimal platinum doublet regimen in elderly patients with non-small-cell lung cancer (NSCLC) is still uncertain. We conducted a randomized phase II study to compare the efficacy and safety of weekly paclitaxel combined with carboplatin with those of the standard schedule.

Patients and methods: Elderly patients (age ≥70 years) with advanced NSCLC were randomly assigned to either the weekly arm {70 mg/m^2 paclitaxel on days 1, 8, and 15 and carboplatin [area under the curve (AUC) = 6] on day 1} or the standard arm [200 mg/m^2 paclitaxel and carboplatin (AUC = 6) on day 1]. The primary end point was the overall response rate (ORR).

Results: Eighty-two patients were enrolled. The ORR and median progression-free survival were 55% and 6.0 months for the weekly arm and 53% and 5.6 months for the standard arm. Grade 3/4 neutropenia and peripheral neuropathy were observed in 41% and 0% of the patients in the weekly arm and in 88% and 25% in the standard arm, respectively.

Conclusions: This is the first randomized study that compares the platinum doublet designed specifically for the elderly. Regarding the safety, the weekly regimen was less toxic than the standard regimen and seems to be preferable for elderly patients with advanced NSCLC.

Key words: elderly patients, non-small-cell lung cancer, weekly paclitaxel

original article

introduction

Lung cancer is the leading cause of cancer deaths in most of the developed countries. More than 80% of the patients with lung cancer have non-small-cell histology and ~40% of the patients present at stage IIIB or stage IV of the disease at diagnosis [1, 2]. For these patients with advanced non-small-cell lung cancer (NSCLC), platinum-based combinations have been accepted as the standard of care on the basis of their survival benefit [3–5]. In particular, the combination of carboplatin and paclitaxel is the most commonly used regimen for the treatment of advanced NSCLC and has been selected as the reference arm in several phase III trials [6, 7]. With regard to the carboplatin and paclitaxel combination, peripheral neuropathy, myalgia, arthralgia, and myelosuppression are the major clinical conditions that distress patients and sometimes lead to treatment withdrawal. To minimize the occurrence of these toxic effects and to improve the tolerability of this regimen, weekly schedule of paclitaxel has been evaluated and found to be associated with a reduction in the treatment toxicity and feasible therapeutic indices for patients with advanced NSCLC although these studies mainly included younger patients and the benefit of such a regimen for elderly patients remains unknown [8–10].

The benefit of platinum doublet chemotherapy for the elderly is still controversial. Some investigators recommend single-agent chemotherapy with new-generation chemotherapeutic agents such as vinorelbine or gemcitabine on the basis of the evidences from some phase III trials [11–13]; on the other hand, others consider that platinum doublet chemotherapy is also acceptable for elderly patients, although the frequency and severity of toxic effects associated with the latter are generally high [14].

Correspondence to: Dr T. Sakakibara, Department of Respiratory Medicine, Tohoku University Hospital, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan.
Tel: +81-22-717-8539; Fax: +81-22-717-8549; E-mail: sakatomo@idac.tohoku.ac.jp

In this context, we previously conducted an elderly-specific phase II study of weekly paclitaxel combined with carboplatin, which demonstrated a reasonable response rate (45%) and less severe toxic effects (e.g. a grade 3 peripheral neuropathy rate of 3%) [15]. Next, we planned the current randomized phase II trial that involved weekly paclitaxel combined with carboplatin and compared it with standard triweekly regimen of paclitaxel combined with carboplatin for elderly patients with advanced NSCLC; this was done in order to select a proper regimen for future phase III studies that compare the efficacy of platinum doublet chemotherapy with that of single-agent chemotherapy.

patients and methods

selection of patients

Patients (age ≥70 years) with cytologically or histologically confirmed stage IIIB, stage IV, or postoperative recurrent NSCLC with measurable lesions who had never received chemotherapy or radiotherapy were enrolled in this study. Further, patients were also required to satisfy the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of zero to one, an estimated life expectancy exceeding 12 weeks, white blood cell (WBC) count of >4000/mm^3 (or a neutrophil count of >2000/mm^3), hemoglobin levels of >9.0 g/dl, platelet count of >100 000/mm^3, serum total bilirubin level of <1.5 mg/dl, serum levels of aspartate aminotransferase and alanine aminotransferase <2.0× the institutional upper limit of the normal range, serum creatinine levels of <1.5 mg/dl, and pO_2 level of >60 mmHg. We excluded patients with symptomatic brain metastasis or severe comorbidities such as symptomatic cardiovascular disease, liver cirrhosis, radiographically obvious pulmonary fibrosis, acute peptic ulcer, uncontrolled diabetes, and peripheral neuropathy. The institutional review boards of all the nine hospitals approved this study, and a written informed consent was obtained from all the enrolled patients.

treatment schedule

The enrolled patients were stratified by clinical stage (IIIB, IV, or postoperative recurrence) or ECOG PS (0 or 1) at baseline and then randomly assigned to receive the weekly paclitaxel with carboplatin arm (W arm), in which 70 mg/m^2 paclitaxel was administered once a week on days 1, 8, and 15 with carboplatin [area under the curve (AUC) = 6] on day 1 of each week, or the standard paclitaxel with carboplatin arm (S arm), in which 200 mg/m^2 of paclitaxel was administered with carboplatin (AUC = 6). Before the administration of paclitaxel, the patients were premedicated with dexamethasone (8 mg i.v.), ranitidine (50 mg i.v.), and diphenhydramine (50 mg orally) to prevent anaphylactic reaction. Carboplatin was administered immediately after paclitaxel. No prophylactic granulocyte colony-stimulating factor or prophylactic antibiotic support was planned. Paclitaxel was administered to the patients of the W arm on days 8 and 15 when the neutrophil and platelet counts exceeded 1000/mm^3 and 75 000/mm^3, respectively. The following dose reductions in the subsequent cycles were permitted in cases with the following toxic effects according to protocol: the paclitaxel dosage was reduced to 60 mg/m^2 in the W arm or 180 mg/m^2 in the S arm in case of febrile neutropenia, grade 4 neutropenia lasting 4 days, grade 2 or worse peripheral neuropathy, myalgia, or arthralgia, or grade 3 or worse non-hematological toxic effects other than nausea, vomiting, and appetite loss. Further, carboplatin was reduced to AUC 5.0 in both the arms when the platelet count decreased to <20 000/mm^3, serum creatinine levels exceeded 1.5× the institutional upper limit of the normal level, or grade 3 or worse non-hematological toxic effects were observed. To initiate subsequent cycles, the prerequisite conditions were as follows: a WBC count of >3000/mm^3 (or a neutrophil count of >1500/mm^3), platelet count of >100 000/mm^3, or non-hematological toxic effects below grade 2. A delay of the protocol treatment due to toxicity was permitted until 3 weeks. All the patients were required to receive the protocol treatment for at least three cycles unless the disease progressed, unacceptable toxicity occurred, the patients refused further treatment, or the physician decided to discontinue the treatment. Second-line chemotherapy or other treatments after this study were not prohibited by the protocol.

treatment assessment

Baseline assessment included a physical examination, complete blood counts (CBC) with differential and platelet count, hepatic and renal function tests, urine analysis, 12-lead electrocardiogram, and chest radiography. Tumor evaluation was carried out at the baseline by either a computed tomography (CT) scan or magnetic resonance imaging. During the study, the medical history and results of physical examination, weight, vital signs, ECOG PS, CBC, blood chemistry, and chest radiography were monitored on a weekly basis. Radiographic evaluation by CT scan was carried out at least every two cycles to assess the patient's response to the treatment. Unidirectional measurements were undertaken according to the RECIST criteria. The definitions of complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD) are as follows: CR, disappearance of all target lesions; PR, at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters; PD, at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study or the appearance of one or more new lesions; SD, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. The confirmation of CR and PR required response duration of ≥4 weeks, while the confirmation of stable disease required response duration of ≥6 weeks after the initiation of the treatment. Toxic effects were assessed according to the National Cancer Institute—Common Toxicity Criteria version 2.0.

statistical analysis

The primary end point of this study was the overall response rate (ORR), and the secondary end points were the progression-free survival (PFS), overall survival, and toxicity profile. The sample size was calculated independently for each arm as follows. Assuming that an ORR of 40% in eligible patients would indicate potential usefulness, while an ORR of 20% would constitute the lower limit of interest, with $\alpha = 0.05$ and $\beta = 0.2$, the estimated accrual was 36 in each arm. Fisher's exact test was used to estimate the correlation among the different variables of the two arms. The estimation of survival was carried out using the Kaplan–Meier method and the log-rank test.

results

patient characteristics

From November 2004 to June 2007, 82 patients were enrolled from nine institutions in this study (Table 1). The median age of the patients at the time of enrollment was 75 years (range 70–87 years); 57% of the patients were ≥75 years and 15% of the patients were ≥80 years. Of the 82 patients, 69 (84%) were male and 40 (49%) had PS of one. Adenocarcinoma and squamous cell carcinoma were the most common histological types and were observed in 47% and 41% of the patients, respectively. There were 26 (31%) patients with stage IIIB, 47 (57%) with stage IV, and 9 (11%) with postoperative recurrence. There was no statistical difference in the patient characteristics of the two arms. The median number of cycles of the treatment was three cycles (range 1–6) in each arm, and

75% of the patients underwent three or more cycles in each arm. In the weekly arm, 42 patients received 139 cycles in total. Among 417 planned administrations of paclitaxel, 31 were skipped mainly because of temporary toxicity and 93% of planned doses were actually administered.

response and survival

The ORR (CR + PR) observed for the W and S arms were 55% [95% confidence interval (CI) 40% to 70%] and 53% (95% CI 38% to 68%), respectively (Table 2). There was no statistical difference in the response of the patients in the two arms. One patient in the W arm could not be evaluated for the response because the patient died due to treatment-related effects before the first evaluation of the efficacy. The median PFS and median survival time (MST) were 6.0 and 14.7 months for the patients of the W arm and 5.6 and 15.5 months for the patients of the S arm, respectively (Figure 1).

Table 1. Patient characteristics according to the treatment group

Characteristics	Weekly ($N = 42$)	Standard ($N = 40$)	Total ($N = 82$)
Age, years			
Median	74	75	75
Range	70–83	70–87	70–87
Sex			
Male	38	31	69
Female	4	9	13
ECOG PS			
0	21	21	42
1	21	19	40
Stage			
IIIB	13	13	26
IV	25	22	47
Postoperative recurrence	4	5	9
Type of histology			
Adenocarcinoma	22	17	39
Squamous cell carcinoma	15	19	34
Large cell carcinoma	4	2	6
Others	1	2	3
Number of treatment cycles			
Median	3	3	3
Range	1–6	1–6	1–6

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Response and survival according to the treatment group

	Weekly ($N = 42$), n (%)	Standard ($N = 40$), n (%)
Response		
Complete response	1 (2)	0 (0)
Partial response	22 (53)	21 (53)
Stable disease	15 (36)	14 (35)
Progressive disease	3 (7)	5 (12)
Not evaluable	1 (2)	
Overall response rate (%) (95% CI)	55 (40–70)	53 (38–68)
Disease control rate (%) (95% CI)	90 (81–99)	88 (78–98)

CI, confidence interval.

toxicity

The treatment-related grade 2 or worse toxic effects observed in this study are summarized in Table 3. Neutropenia was the most common hematological toxicity in both arms, and grade 3 or 4 neutropenia was observed in 41% and 88% of the patients in the W and S arms, respectively ($P < 0.0001$). Febrile neutropenia was observed in 2% and 10% of the patients in the W and S arms, respectively. Grade 3 peripheral neuropathy was observed in 0% and 25% of the patients in the W and S arms, respectively ($P = 0.018$). Myalgia and arthralgia also tended to be severe in the patients of the S arm. Although other non-hematological toxic effects observed were almost moderate and manageable, there was one treatment-related death in the W arm owing to drug-induced interstitial lung disease.

discussion

Although the number of elderly patients with advanced NSCLC has been increasing, the standard of care for such patients remains controversial. Randomized phase III studies of single-agent chemotherapy with drugs such as vinorelbine or gemcitabine demonstrated that the survival benefit for elderly NSCLC patients treated with this modality was higher than that

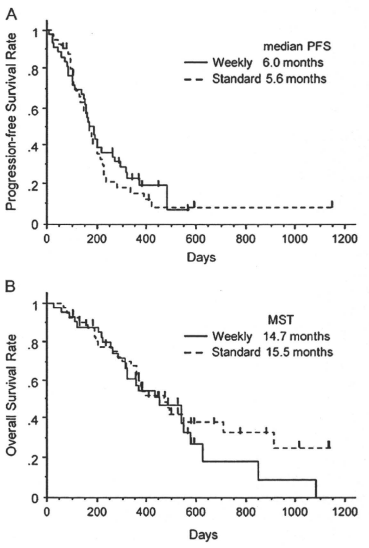


Figure 1. Progression-free survival (PFS) (A) and overall survival (B) rate in each arm.

doi:10.1093/annonc/mdp401 | 3

Table 3. Adverse events (≥grade 2) according to the treatment group

Toxicity	Weekly ($N = 42$)				Standard ($N = 40$)				
	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)	
Hematological									
Neutropenia	13	14	3	41	0	11	24	88	*
Thrombocytopenia	4	2	1	7	4	2	1	8	
Anemia	13	11	1	29	16	8	0	20	
Non-hematological									
Febrile neutropenia	–	1	0	2	–	4	0	10	**
Peripheral neuropathy	5	0	0	0	7	10	0	25	
Arthralgia, myalgia	1	0	0	0	4	3	0	8	
Hyponatremia	–	2	0	5	–	5	0	13	
Fatigue	0	1	0	2	4	0	0	0	
Nausea/vomiting	4	2	0	5	11	5	0	13	
Diarrhea	0	1	0	2	2	0	0	0	
Constipation	0	1	0	2	0	0	0	0	
Rash	2	0	0	0	2	0	0	0	
Infection	6	2	0	2	3	2	0	5	
Pneumonitis	0	0	1[a]	2	0	1	0	3	
Dizziness	0	0	0	0	1	1	0	3	
Cerebral infarction	0	0	0	0	0	0	1	3	

[a]Treatment-related death.

*$P < 0.0001$.

**$P = 0.018$.

of the best supportive treatment [11, 12]. In addition, a recent Japanese study has indicated that docetaxel monotherapy is also suitable for elderly NSCLC patients, although the extremely high efficacy (an MST of 14.3 months) should be reexamined by another confirmatory study [13]. On the other hand, there has been no randomized study of platinum doublet chemotherapy specifically targeting the elderly population. Some retrospective analyses conducted on the subgroup of the elderly from several trials without an upper age limit have documented the benefits of platinum-based combination chemotherapy in those patients with good PS [14]. However, the percentage of the elderly population enrolled in those trials was only 30%–40%, which is much lesser than that of general practice, indicating that a selection bias clearly exists in the enrollment of elderly patients into such clinical trials in which there is no upper limit for the age of the patients. Moreover, even in those selected elderly patients with good PS, toxic effects tend to be more severe than those in younger patients, thus clearly indicating the need for elderly-specific clinical trials [16].

In this study, the patients of both the W and the S arms met the primary end point, indicating that the combination treatment of paclitaxel and carboplatin with each schedule is effective for elderly NSCLC patients. The survival data (PFS and MST) were also similar between the two arms, both of which are comparable to the results of previous trials of platinum doublet chemotherapy conducted in younger patients [3–7]. The tendency of efficacy and safety results of our study was similar to those of the phase III by Belani which also compared carboplatin plus weekly paclitaxel with carboplatin plus standard paclitaxel although most patients were <70 years old and the dose of weekly paclitaxel (100 mg/m^2/week) and the additional maintenance therapy of paclitaxel were different from our study. More than half of the patients included in our study were >75 years old which is similar to the population of elderly patients in general practice. Thus, we believe, at least for patients with good PS, the platinum doublet regimen is a reasonable choice even if they are >75 years old. Regarding the toxic effects, the incidence of grade 3/4 neutropenia and febrile neutropenia in the patients of the W arm was apparently lower than that in the patients of the S arm. The peripheral neuropathy observed in the patients of the W arm was also significantly mild and manageable as compared with that in the patients of the S arm. The results of the efficacy and safety of the present regimen comprising weekly paclitaxel were comparable to those observed in our previous study and other studies [8–10, 15, 17]. Its safety profile, in particular, is the greatest strength that may benefit elderly patients with less tolerance to chemotherapy.

Recently, Ramalingam et al. [18] reported the results of subset analysis from Belani's study specifically targeted for elderly population. Very similar to our study, they also concluded that regimen with weekly paclitaxel was equally effective and less toxic than that with standard paclitaxel in the elderly population, although the response rate of weekly regimen was less than that in our study (26% versus 55%). There are also some differences in toxic effects between the weekly regimens of each study. For example, incidences of grade 3 neuropathy, grade 3 or worse neutropenia, and anemia were 5.5%, 17%, and 16%, respectively, in Ramalingam study; meanwhile, those incidences in our study were 0%, 41%, and 29%, respectively. As to the neuropathy, dosage of paclitaxel and the maintenance therapy might have influenced the result. On the other hand, the difference of hematological toxic effects

might depend on some genetic difference between USA and Japanese patients because recent large common-arm analysis between United States and Japan revealed that Japanese patients suffered from significantly higher hematological toxic effects than USA patients even if treated with similar dose of paclitaxel and carboplatin [19].

The present study has a few limitations. The first limitation is that since the sample size used in this study was small, a definitive conclusion cannot be reached solely on the basis of the findings of this study. However, previous reports support the results obtained for each treatment conducted in this study. Since it is still unclear as to which of the two strategies of platinum doublet chemotherapy and single-agent chemotherapy is superior to the other, a larger comparative study should be conducted in future. We believe that the weekly paclitaxel and carboplatin combination used in this study may be a successful candidate as a proper platinum doublet regimen. The second limitation of this study is that we did not conduct a comprehensive geriatric assessment (CGA) or assess the quality of life of the patients in this study. The difficulty in the treatment of elderly patients is due to the heterogeneity of their comorbidities and organ functions. CGA has been recognized as a very important tool for the evaluation of the general conditions of the elderly patients; this tool must be applied in future trials for the identification and selection of a heterogeneous elderly population [20, 21]. And finally, the superiority between platinum doublet and single-agent chemotherapy in elderly population remains unclear; thus, we are now conducting the next randomized study comparing the current weekly paclitaxel with carboplatin to docetaxel alone.

In conclusion, this is the first randomized study that analyzed the efficacy and safety of the platinum doublet chemotherapy specifically designed for the elderly. In this study, the efficacy of both the treatment regimens consisting of paclitaxel and carboplatin was similar. Regarding the safety, the regimen comprising weekly paclitaxel was less toxic than that with the standard paclitaxel dosage and seems to be preferable for elderly patients with advanced NSCLC and is worthy of further investigation.

references

1. Parkin DM. Global cancer statistics in the year 2000. Lancet Oncol 2001; 2: 533–543.
2. Govindan R, Page N, Morgensztern D et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 2006; 24: 4539–4544.
3. Fossella F, Pereira JR, von Pawel J et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non–small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003; 21: 3016–3024.
4. Schiller JH, Harrington D, Belani CP et al. Comparison of four chemotherapy regimens for advanced non–small-cell lung cancer. N Engl J Med 2002; 346: 92–98.
5. Ohe Y, Ohashi Y, Kubota K et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007; 18: 317–323.
6. Sandler A, Gray R, Perry MC et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006; 355: 2542–2550.
7. Kubota K, Kawahara M, Ogawara M et al. Japan Multi-National Trial Organisation. Vinorelbine plus gemcitabine followed by docetaxel versus carboplatin plus paclitaxel in patients with advanced non-small-cell lung cancer: a randomised, open-label, phase III study. Lancet Oncol 2008; 9: 1135–1142.
8. Belani CP, Barstis J, Perry MC et al. Multicenter, randomized trial for stage IIIB or IV non–small-cell lung cancer using weekly paclitaxel and carboplatin followed by maintenance weekly paclitaxel or observation. J Clin Oncol 2003; 21: 2933–2939.
9. Hirabayashi M, Endoh K, Teramachi M et al. Phase II study of carboplatin and weekly paclitaxel combination chemotherapy in advanced non-small cell lung cancer: a Kansai Clinical Oncology Group study. Lung Cancer 2004; 44: 355–362.
10. Belani CP, Ramalingam S, Perry MC et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non–small-cell lung cancer. J Clin Oncol 2008; 26: 468–473.
11. The Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. J Natl Cancer Inst 1999; 91: 66–72.
12. Gridelli C, Perrone F, Gallo C et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 2003; 95: 362–372.
13. Kudoh S, Takeda K, Nakagawa K et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non–small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 2006; 24: 3657–3663.
14. Langer CJ, Manola J, Bernardo P et al. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. J Natl Cancer Inst 2002; 94: 173–181.
15. Inoue A, Usui K, Ishimoto O et al. A phase II study of weekly paclitaxel combined with carboplatin for elderly patients with advanced non-small cell lung cancer. Lung Cancer 2006; 52: 83–87.
16. Jatoi A, Hillman S, Stella P et al. Should elderly non-small-cell lung cancer patients be offered elderly-specific trials? Results of a pooled analysis from the North Central Cancer Treatment Group. J Clin Oncol 2005; 23: 9113–9119.
17. Pujol JL, Milleron B, Molinier O et al. Weekly paclitaxel combined with monthly carboplatin in elderly patients with advanced non-small cell lung cancer: a multicenter phase II study. J Thorac Oncol 2006; 1: 328–334.
18. Ramalingam S, Perry MC, La Rocca RV et al. Comparison of outcomes for elderly patients treated with weekly paclitaxel in combination with carboplatin versus the standard 3-weekly paclitaxel and carboplatin for advanced nonsmall cell lung cancer. Cancer 2008; 113: 542–546.
19. Gandara DR, Kawaguchi T, Crowley J et al. Japanese-US common-arm analysis of paclitaxel plus carboplatin in advanced non-small-cell lung cancer: a model for assessing population-related pharmacogenomics. J Clin Oncol 2009; 27: 3540–3546.
20. Hensing TA, Peterman AH, Schell MJ et al. The impact of age on toxicity, response rate, quality of life, and survival in patients with advanced, Stage IIIB or IV nonsmall cell lung carcinoma treated with carboplatin and paclitaxel. Cancer 2003; 98: 779–788.
21. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 2007; 25: 1824–1831.

doi:10.1093/annonc/mdp401 | 5

UICC
global cancer control

IJC
International Journal of Cancer

Frequency of and variables associated with the EGFR mutation and its subtypes

Tomoaki Tanaka[1], Masaru Matsuoka[2], Akihisa Sutani[3], Akihiko Gemma[4], Makoto Maemondo[5], Akira Inoue[6], Shoji Okinaga[7], Makoto Nagashima[8], Satoshi Oizumi[9], Kazutsugu Uematsu[1], Yoshiaki Nagai[3], Gaku Moriyama[1], Hitoshi Miyazawa[1], Kenji Ikebuchi[2], Satoshi Morita[10], Kunihiko Kobayashi[3] and Koichi Hagiwara[1]

[1] Department of Respiratory Medicine, Saitama Medical University, Saitama, Japan
[2] Central Laboratory, Saitama Medical University, Saitama, Japan
[3] Department of Respiratory Medicine, Saitama Medical University International Medical Center, Saitama, Japan
[4] Department of Internal Medicine, Division of Pulmonary Medicine, Infectious Disease and Oncology, Nippon Medical School, Tokyo, Japan
[5] Department of Respiratory Medicine, Miyagi Cancer Center, Miyagi, Japan
[6] Department of Respiratory Medicine, Tohoku University Hospital, Sendai, Japan
[7] Department of Respiratory Medicine, Kesennuma City Hospital, Miyagi, Japan
[8] Department of Surgery, Toho University Sakura Medical Center, Chiba, Japan
[9] First Department of Medicine, Hokkaido University, School of Medicine, Sapporo, Japan
[10] Department of Biostatistics and Epidemiology, Yokohama City University Medical Center, Kanagawa, Japan

Mutation in the epidermal growth factor receptor (EGFR) is frequently seen in non-small cell lung cancers (NSCLCs), especially in Asian females with adenocarcinoma. The frequency of mutation and the factors associated requires to be elucidated by analyzing a large number of consecutive clinical samples. We summarized the result of the EGFR mutation analysis for 1,176 patients performed at the time of diagnosis or relapse. The PNA-LNA PCR clamp, a highly sensitive detection method for the EGFR mutation, was employed. For fresh cases a portion of samples isolated to establish the diagnosis of lung cancer was used. For cases with a relapsed disease archival tissue were tested. The variables associated with the EGFR mutation after removing the confound factors were investigated by the logistic analysis using the samples collected in our university (n = 308) where detailed information on patients were available. The frequency of the EGFR mutation and its subtypes were investigated using all samples (n = 1,176). The EGFR mutation was significantly associated with adenocarcinoma (p = 0.006) and light-smoking (p < 0.0001), but not gender. The deletions in exon 19 were more frequently associated with male gender while exon 21 deletions were with female gender (p = 0.0011). The overall frequency of the EGFR mutation was 31%. Our result suggests that the female predominance in the EGFR mutation rate is a reflection of a higher frequency of adenocarcinoma in females. The gender difference in the mutation subtypes may provide a clue for the mechanism of the occurrence of the EGFR mutation.

EGFR mutation is one of the most common genetic alterations in non-small cell lung cancers (NSCLCs).[1,2] It is more frequently seen in East Asians, females and non-smokers.[3] EGFR mutation is more frequently found in adenocarcinomas than in other types of cancers.[4] Since adenocarcinomas occur more frequently in females than in males, the seeming gender difference in the EGFR mutation rate may just reflect the gender difference in the rate of adenocarcinoma. The epidemiological factors associated with the EGFR mutations provide the clues to the causes that originated EGFR mutation and hence cancers. Therefore, it is important to eliminate the confounding factors and identify the factor(s) that are primarily associated with EGFR mutations. A study consisting of a large number of patients is required.

The PNA-LNA PCR clamp is a highly sensitive detection method for EGFR mutation.[5,6,7] It detects mutations in the presence of 100 to 1000-fold background of the normal cells over the cancer cells, and thus enables one to detect the EGFR mutation from cytological specimens used to diagnose cancers in clinical practice.[6] Several prospective phase II studies have shown the administration of gefitinib to the EGFR mutation-positive patients to provide a survival benefit.[8,9,10–13] Even patients with a poor performance status have been shown to benefit from gefitinib if they are mutation-positive.[14] With this information, a test for the EGFR mutation for NSCLC patients has become routine in Japan. Currently more than 10,000 NSCLC patients per year are tested for EGFR mutations by the PNA-LNA PCR clamp.

Grant sponsor: A grant-in-aid for scientific research from the Japan Society for the Promotion of Science; **Grant number:** 19790567
DOI: 10.1002/ijc.24746
History: Received 19 Mar 2009; Accepted 30 Jun 2009; Online 16 Jul 2009
Correspondence to: Koichi Hagiwara, Department of Respiratory Medicine, Saitama Medical University, 38 Morohongo, Moroyama-machi, Saitama, 350-0495, Japan, Fax: +81-49-276-1192, E-mail: hagiwark@saitama-med.ac.jp

Since the development of the PNA-LNA PCR clamp in 2005, we have tested for EGFR mutations in all NSCLC patients who visited our hospital and provided informed consent. In addition, we tested for the mutation in more than 2,000 samples sent from more than 20 collaborative institutes; most of the samples were a part of a specimen isolated in order to establish the diagnosis of lung cancer. We herein summarize the results of tests and the statistical analyses for the first consecutive 1,176 patients.

Material and Methods

Clinical samples

This study was approved by the institutional review board of each institute and performed in accordance with the Declaration of Helsinki (1995, revised in Edinburgh 2000). An aliquot of the specimens which were isolated to establish the diagnosis of NSCLC, or in the case of relapsed diseases, the archival specimens from the previous treatment were subjected to the EGFR mutation test by the PNA-LNA PCR clamp after obtaining informed consent from all patients. The period of sample collection for Saitama Medical University Hospital and Saitama Medical University International Medical Center ranged from October 2004 to February 2008, while that for the collaborative institutes differed depending on the time they joined to the study.

EGFR mutation analyses

Each sample (sputum, pleural effusion, bronchial washing, needle biopsy and paraffin embedded tissue) was divided into two parts immediately after collection at each institute. When the diagnosis of cancer was pathologically established from the first part, the other part was sent to our institute to test for the EGFR mutation by the PNA-LNA PCR clamp. The investigated gefitinib sensitive mutations included G719C, G719S, G719A, L858R, L861Q and exon 19 deletions, as well as a gefitinib resistant mutation T790M. The results were reported within 1 to 3 days after the receipt of the samples so that each institute was able to utilize the results in order to select the appropriate treatment for each patient.

Statistical analysis

Any significant differences among the categorized groups were compared using either the two-sided χ^2 test or Fisher's exact test. The adjusted effects of age, sex, histology, staging and smoking history on EGFR mutation were evaluated by using a logistic regression model, and the results were described as an odd ratio with a 95% confidence interval. All analyses were performed using SPSS Statistics (SPSS version 17.0 for Windows, SPSS Inc, Chicago, IL).

Results

Samples

We were able to collect detailed information for the samples collected in our university. On the other hand, because of the privacy policy of the individual institutes, information was incomplete for the samples from other institutes. Therefore, we performed two different analyses. Firstly, we analyzed the samples collected in our university, and performed detailed analyses on the factors associated with EGFR mutations and their subtypes. Next, we put all samples together and calculated the frequencies of EGFR mutations and their subtypes.

Table 1. *EGFR* mutation identified

	No. of samples	Male	Female
Exon 18 point mutation	1		
G719S	1	0	1
Exon 19 deletions	68		
E746-A750del Type1	25	13	12
E746-A750del Type2	14	4	10
L747-A750del T751S	1	0	1
L747-S752del P753S	10	6	4
L747-E749del A750P	3	2	1
L747-T751del	10	7	3
L747-T751del insA	1	1	0
L747-S752del P753Q	1	1	0
E746-S752del insV	1	1	0
E746-A750del insKP	1	1	0
E746-T751del insLS	1	1	0
Exon 19 deletions + Exon 21 point mutation	1		
L747-T751del + L858R	1	0	1
Exon 19 deletions + Exon 20 point mutation	2		
E746-A750del Type1 + T790M	1	0	1
E746-A750del Type2 + T790M	1	1	0
Exon 21 point mutations	38		
L858R	37	14	23
L861Q	1	0	1
Exon 21 point mutation + Exon 20 point mutation	2		
L858R + T790M	2	0	2
Total	112	52	60

EGFR mutations found in 112 patients out of 308 patients who visited to Saitama Medical University or Saitama Medical University International Medical Center were summarized. Sources of the samples include bronchial washing/brushing, 167; pleural effusion, 42; sputum, 22; pleural effusion, 2; paraffin embedded tissue, 69; and surgically resected tissue, 9. A part of the data has been reported elsewhere.[6,7] E746-A750del Type1: E746-A750del (2235-2249del). E746-A750del Type 2: E746-A750del (2236-2250del).

Detailed analysis

We had 311 patients who visited to our university and were tested for the EGFR mutation, and 308 of them provided informative results. The source of the samples included all types of cytological and tissue specimens that are used for the diagnosis of the cancer. A total of 112 (36.4%) had EGFR mutations (Table 1). We identified the gefitinib resistant

Table 2. Association of each variable with the *EGFR* mutation

Sex	Negative	Positive	χ^2 value	*P*-value
Male	155	52	33.015	<0.0001
Female	41	60		
Histology				
Adenocarcinoma or Adeno-squamous cell carcinoma	138	104	20.201	<0.0001
Squamous cell carcinoma and others	58	8		
Smoking history*				
Less than 20 pack-year or never	37	59	41.398	<0.0001
More than 20 pack-year	150	43		
Age				
Younger than 65 years	70	54	4.125	0.0423
Older than 65 years	126	58		
Clinical stage				
Stage I-II	27	12	0.612	0.7364
Stage III-IV	146	86		
Post-operative	23	14		

*Nineteen patients who had unknown smoking history were excluded.

Table 3. Logistic regression analysis for the association with EGFR mutation ($N = 289$)

		Odds ratio (95% confidence interval)	*P*-value
Age	less than 64 yrs/ over 65 yrs	1.57 (0.90–2.70)	0.12
Gender	Male/female	0.69 (0.35–1.38)	0.30
Histology	Adenocarcinoma and adenosquamous carcinoma/squamous cell carcinoma and others	3.18 (1.39–7.23)	0.006
Smoking history	Packs a year < 20/20 ≤ packs a year	3.84 (1.92–7.65)	<.0001
Stage	Stages I and II/Stages III and IV	0.84 (0.37–1.90)	0.67

Nineteen patients who had unknown smoking history were excluded.

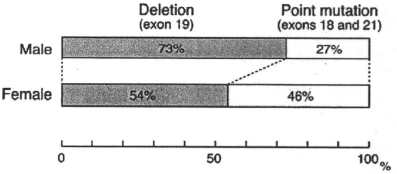


Figure 1. The type of EGFR mutations according to gender. The exon 19 deletions are more frequently found in males than in females (Fisher's exact test, $p < 0.047$).

Table 4. Logistic regression analysis for the association with exon 19 deletion (N=102)

		Odds ratio (95% confidence interval)	*P*-value
Age	less than 64 yrs/ over 65 yrs	2.16 (0.87–5.36)	0.10
Gender	Male/female	5.10 (1.92–13.54)	0.0011
Histology	Adenocarcinoma and adenosquamous cell carcinoma/squamous cell carcinoma and others	2.26 (0.43–11.8)	0.34
Smoking history	pcyear < 20/20 ≤ pcyear	0.64 (0.25–1.64)	0.35
Stage	Stage III to IV/ Stage I to II	2.94 (0.67–12.8)	0.15

Ten patients who had unknown smoking history were excluded.

mutation T790M in 4 samples, for all of which the gefitinib sensitive mutations co-existed. All patients from whom these samples were isolated had been treated by gefitinib. Patients who were not previously treated with gefitinib did not have the T790M mutation.

We investigated the association of several variables with the EGFR mutation (Table 2). Two-sided χ^2 tests revealed gender (female), histology (adenocarcinoma and adenosquamous cell carcinoma) and smoking history (less than 20 packs/year) to be significantly associated with the presence of the EGFR mutation.

The variables studied here may be associated with each other, and they may act as confounding factors in the analyses of other variables. For example, the smoking rate is several-fold different between males and females in Japan and thus the variables affected by smoking may show a seeming gender difference. To eliminate the effect of such confounding variables, we performed a logistic regression analysis (Table 3). The analysis revealed histology and smoking history to be significantly associated with EGFR mutation, while gender, which has often been used as a criterion for selecting a patient group populated with EGFR mutations in clinical medicine, was not significantly associated.

In a subgroup analysis where only mutation-positive patients were studied, we noticed that exon 19 deletions were more frequently found in males, and the difference was significant according to Fisher's exact test (Figure 1). We again performed a logistic regression analysis and confirmed that exon 19 deletions were significantly associated with a male gender after removing the influence of other variables (Table 4). We concluded that not the frequency of the EGFR mutation but the subtype of it shows a gender difference.

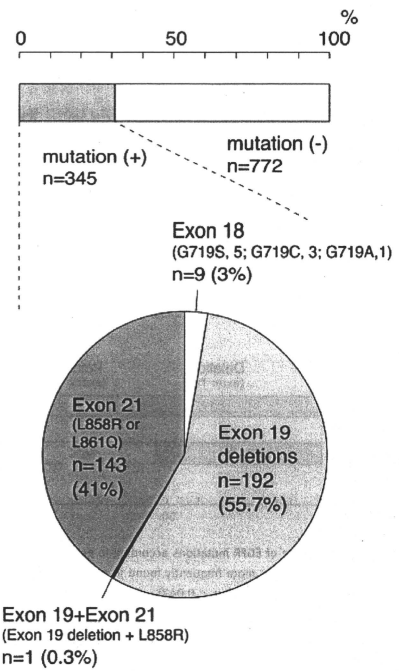


Figure 2. The rate of EGFR mutations. A total of 1176 samples were analyzed, of which 1120 samples provided informative results. Of the 56 uninformative samples, 52 were paraffin-embedded tissues. The number of paraffin-embedded tissue specimens examined was 344, meaning that about 1/8 of them were not suitable for the mutation analysis.

Frequency of the EGFR mutation

The results of the EGFR mutation analysis where samples from our university and those from other institutes were combined are shown in Figure 2. Out of 1176 samples, 1120 samples provided informative results. The EGFR mutation rate was 31%, which was very similar to the rate obtained in the detailed analysis described above.

Discussion

Our result shows the rate of EGFR mutations to be 43% in adenocarcinoma and 12% in the other types of NSCLCs. The overall frequency of EGFR mutations was around 30% in both the samples studied in detail and in all the samples combined. We are in the field of internal medicine, as are our collaborators, and therefore advanced cancers are preferably referred to us. Our samples may better represent those from more advanced stages of NSCLCs. Instead, the frequency was found to be consistent with what determined using surgical samples[3,15,16] which may better represent earlier stages of NSCLCs. Our results suggest that the rate of the EGFR mutation is similar irrespective of the stages of NSCLCs.

The results showing EGFR mutation to be associated with adenocarcinoma but not gender are considered to have clinical implications. Under a setting where an EGFR mutation test is not readily available, the targets for gefitinib therapy have been determined based on the patient characteristics and one of the criteria frequently employed has been adenocarcinomas which occurred in females. According to our results, there is no reason to select the patients by gender.

In contrast to the rate of the EGFR mutations, the mutation subtypes showed a gender difference. Although the exact mechanism by which each subtype occurs has not yet been elucidated, chromosomal recombination that involves DNA double strand breaks and repairs is likely to be involved in exon 19 deletions. It is well known that the meiotic recombination rate shows a clear gender difference.[17] Instead, to our knowledge, there have been no reports showing a gender difference in the rate of somatic, chromosomal deletion mutations. The EGFR mutation may therefore be an interesting model to pursue the gender difference of cancers from the viewpoint of the DNA repair mechanisms.

In the current study, we reported the result of 1176 samples and found a close association between adenocarcinoma and EGFR mutations as well as the gender difference in the mutation subtypes. We also provided the frequencies of EGFR mutations in the samples that are considered to better represent the later stages of NSCLCs. Since tests for EGFR mutations are now widely performed, studies consisting of a large number of samples are now becoming realistic. Such studies will provide further valuable information on the genesis of EGFR mutations.

Acknowledgements

The authors thank Ms. Chieko Ono for technical assistance.

The following hospitals contributed to the study: Asahikawa Medical College (Yoshinobu Ohsaki), Dohoku National Hospital (Yuka Fujita), Fukushima Medical University (Takashi Ishida), Hokkaido Social Insurance Hospital (Toshiyuki Harada), KKR Sapporo Medical Center (Hiroshi Isobe, Testuya Kojima), Toranomon Hospital (Kunihiko Yoshimura), Kanto Medical Center NTT EC (Kazuhiro Usui), Kanagawa Cardiovascular and Respiratory Center (Takashi Ogura), Sapporo General Hospital (Shigeaki Ogura), Nippon Medical School Chiba Hokusoh Hospital (Mitsunori Hino), Hokkaido University Graduate School of Medicine (Ichiro Kinoshita), Japanese Red Cross Sendai Hospital (Makoto Miki), National Hospital Organization Hokkaido Cancer Center (Masao Harada), Sendai Medical Center (Hiroshi Miki).

References

1. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129–39.
2. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304: 1497–500.
3. Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T. Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. *Cancer Res* 2004;64: 8919–23.
4. Mitsudomi T, Kosaka T, Yatabe Y. Biological and clinical implications of EGFR mutations in lung cancer. *Int J Clin Oncol* 2006;11:190–8.
5. Nagai Y, Miyazawa H, Huqun, Tanaka T, Udagawa K, Kato M, Fukuyama S, Yokote A, Kobayashi K, Kanazawa M, Hagiwara K. Genetic heterogeneity of the epidermal growth factor receptor in non-small cell lung cancer cell lines revealed by a rapid and sensitive detection system, the peptide nucleic acid-locked nucleic acid PCR clamp. *Cancer Res* 2005;65:7276–82.
6. Tanaka T, Nagai Y, Miyazawa H, Koyama N, Matsuoka S, Sutani A, Huqun, Udagawa K, Murayama Y, Nagata M, Shimizu Y, Ikebuchi K, et al. Reliability of the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp-based test for epidermal growth factor receptor mutations integrated into the clinical practice for non-small cell lung cancers. *Cancer Sci* 2007;98:246–52.
7. Miyazawa H, Tanaka T, Nagai Y, Matsuoka M, Sutani A, Udagawa K, Zhang J, Hirama T, Murayama Y, Koyama N, Ikebuchi K, Nagata M, et al. Peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp-based detection test for gefitinib-refractory T790M epidermal growth factor receptor mutation. *Cancer Sci* 2008;99:595–600.
8. Asahina H, Yamazaki K, Kinoshita I, Sukoh N, Harada M, Yokouchi H, Ishida T, Ogura S, Kojima T, Okamoto Y, Fujita Y, Dosaka-Akita H, et al. A phase II trial of gefitinib as first-line therapy for advanced non-small cell lung cancer with epidermal growth factor receptor mutations. *Br J Cancer* 2006;95:998–1004.
9. Sutani A, Nagai Y, Udagawa K, Uchida Y, Koyama N, Murayama Y, Tanaka T, Miyazawa H, Nagata M, Kanazawa M, Hagiwara K, Kobayashi K. Gefitinib for non-small-cell lung cancer patients with epidermal growth factor receptor gene mutations screened by peptide nucleic acid-locked nucleic acid PCR clamp. *Br J Cancer* 2006;95:1483–9.
10. Inoue A, Suzuki T, Fukuhara T, Maemondo M, Kimura Y, Morikawa N, Watanabe H, Saijo Y, Nukiwa T. Prospective phase II study of gefitinib for chemotherapy-naive patients with advanced non-small-cell lung cancer with epidermal growth factor receptor gene mutations. *J Clin Oncol* 2006;24:3340–6.
11. Sunaga N, Tomizawa Y, Yanagitani N, Iijima H, Kaira K, Shimizu K, Tanaka S, Suga T, Hisada T, Ishizuka T, Saito R, Dobashi K, et al. Phase II prospective study of the efficacy of gefitinib for the treatment of stage III/IV non-small cell lung cancer with EGFR mutations, irrespective of previous chemotherapy. *Lung Cancer* 2007;56:383–9.
12. Tamura K, Okamoto I, Kashii T, Negoro S, Hirashima T, Kudoh S, Ichinose Y, Ebi N, Shibata K, Nishimura T, Katakami N, Sawa T, et al. Multicentre prospective phase II trial of gefitinib for advanced non-small cell lung cancer with epidermal growth factor receptor mutations: results of the West Japan Thoracic Oncology Group trial (WJTOG0403). *Br J Cancer* 2008;98: 907–14.
13. Yoshida K, Yatabe Y, Park JY, Shimizu J, Horio Y, Matsuo K, Kosaka T, Mitsudomi T, Hida T. Prospective validation for prediction of gefitinib sensitivity by epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer. *J Thorac Oncol* 2007;2: 22–8.
14. Inoue A, Kobayashi K, Usui K, Maemondo M, Okinaga S, Mikami I, Ando M, Yamazaki K, Saijo Y, Gemma A, Miyazawa H, Tanaka T, et al. First-line Gefitinib for Advanced Non-Small Cell Lung Cancer Patients Harboring Epidermal Growth Factor Receptor Mutations without Indication for Chemotherapy. *J Clin Oncol* 2008;27:1394–400.
15. Tokumo M, Toyooka S, Kiura K, Shigematsu H, Tomii K, Aoe M, Ichimura K, Tsuda T, Yano M, Tsukuda K, Tabata M, Ueoka H, et al. The relationship between epidermal growth factor receptor mutations and clinicopathologic features in non-small cell lung cancers. *Clin Cancer Res* 2005;11:1167–73.
16. Sonobe M, Manabe T, Wada H, Tanaka F. Mutations in the epidermal growth factor receptor gene are linked to smoking-independent, lung adenocarcinoma. *Br J Cancer* 2005;93:355–63.
17. Kong A, Gudbjartsson DF, Sainz J, Jonsdottir GM, Gudjonsson SA, Richardsson B, Sigurdardottir S, Barnard J, Hallbeck B, Masson G, Shlien A, Palsson ST, et al. A high-resolution recombination map of the human genome. *Nat Genet* 2002;31:241–7.

original article

Annals of Oncology 21: 800–803, 2010
doi:10.1093/annonc/mdp384
Published online 13 October 2009

A phase II study of amrubicin combined with carboplatin for elderly patients with small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0405

A. Inoue[1]*, O. Ishimoto[2], S. Fukumoto[3], K. Usui[4], T. Suzuki[5], H. Yokouchi[6], M. Maemondo[7], M. Kanbe[8], S. Ogura[9], T. Harada[10], S. Oizumi[11], M. Harada[3], S. Sugawara[2], T. Fukuhara[1] & T. Nukiwa[1]

[1]*Department of Respiratory Medicine, Tohoku University Hospital, Sendai;* [2]*Department of Respiratory Medicine, Sendai Kosei Hospital, Sendai;* [3]*Department of Respiratory Medicine, Hokkaido Cancer Center, Sapporo;* [4]*Department of Respiratory Medicine, Kanto Medical Center NTT-EC, Tokyo;* [5]*Department of Respiratory Medicine, Isawa Hospital, Ohshu;* [6]*Department of Respiratory Medicine, Iwamizawa Rosai Hospital, Iwamizawa;* [7]*Department of Respiratory Medicine, Miyagi Cancer Center, Natori;* [8]*Department of Internal Medicine, Senseki Hospital, Higashi-Matsushima;* [9]*Department of Respiratory Medicine, Sapporo City Hospital, Sapporo;* [10]*Department of Respiratory Medicine, Hokkaido Social Insurance Hospital, Sapporo and* [11]*First Department of Medicine, Hokkaido University School of Medicine, Sapporo, Japan*

Received 22 April 2009; revised 29 June 2009; accepted 30 June 2009

Background: Amrubicin, a new anthracycline agent, has shown high activity for small-cell lung cancer (SCLC) in previous studies. However, a combination regimen with amrubicin and platinum has been investigated little. On the basis of previous phase I study, we conducted this study to evaluate the efficacy and the safety of amrubicin and carboplatin for elderly patients with SCLC.

Methods: Chemotherapy-naive elderly patients with SCLC received amrubicin (35 mg/m^2, days 1–3) and carboplatin [area under the curve (AUC) 4.0, day1] every 3 weeks. The primary end point was overall response rate (ORR), and secondary end points were progression-free survival (PFS), overall survival and toxicity profile.

Results: From January 2005 to November 2007, 36 patients were enrolled [median age 76 (range 70–83); ECOG performance status of zero and one in 17 and 19 patients, respectively]. One complete response and 31 partial responses were observed (ORR 89%). Median PFS was 5.8 months and median survival time was 18.6 months. Grade 3–4 neutropenia was observed in 97% of the patients and six patients (17%) suffered from grade 3–4 febrile neutropenia. Other toxic effects were moderate and treatment-related death was not observed.

Conclusions: Amrubicin combined with carboplatin is quite effective for SCLC with acceptable toxic effects even for the elderly population. Further evaluation of this regimen is warranted.

Key words: amrubicin, carboplatin, chemotherapy, elderly, phase II study, small-cell lung cancer

introduction

Lung cancer is currently a leading cause of cancer death in many countries [1, 2], and small-cell lung cancer (SCLC) accounts for 15%–20% of all lung cancer cases. Over 50% of patients newly diagnosed as SCLC are >70 years old, and the number of elderly patients is expected to increase because the geriatric population is also rapidly growing [3–5]. There has been a general tendency among physicians to consider that elderly patients often have poor tolerance for cisplatin-containing regimens and carboplatin is widely used alternatively because of its mild, non-hematological toxicity [6]. Okamoto et al. [7] had reported that carboplatin plus etoposide is similarly effective as cisplatin plus etoposide in elderly SCLC patients in the Japan Clinical Oncology Group (JCOG) 9702 trial; however, results of the study [the overall response rate (ORR) of 73% and median survival time (MST) of 10.6 months] are not satisfactory, thus it is important to establish a superior treatment regimen for elderly SCLC patients.

Amrubicin is a new anthracycline agent that yielded an extremely high response rate of 79% and MST of 11 months by a dose of 45 mg/m^2 on days 1–3 in chemotherapy-naive SCLC with extensive disease (ED)-SCLC, which was comparable to the results of JCOG 9702 [8]. As to the combination therapy with amrubicin and platinum agent, a phase II study of amrubicin (40 mg/m^2) combined with cisplatin (60 mg/m^2) has also shown promising activity for ED-SCLC; however, most of the enrolled patients in the study were <70 years old [9]. We had previously tried a new combination with amrubicin and

*Correspondence to: Dr A. Inoue, Department of Respiratory Medicine, Tohoku University Hospital, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan. Tel: +81-22-717-8539; Fax: +81-22-717-8549; E-mail: akinoue@idac.tohoku.ac.jp

carboplatin for elderly population as a phase I study that revealed the recommended dose of amrubicin (35 mg/m^2 on days 1–3) and carboplatin (AUC 4.0 on day 1) [10].

Subsequently, we conducted this phase II study to evaluate the efficacy and safety of this regimen for elderly SCLC patients.

methods

patient selection

Patients aged ≥70 years with histologically confirmed SCLC who had never received chemotherapy or radiotherapy were enrolled in this study. Other eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status (PS) of zero or one and estimated life expectancy ≥12 weeks. Laboratory requirements included hemoglobin ≥9 g/dl, white blood cell count ≥4000/mm^3, absolute neutrophil count ≥2000/mm^3, platelets >100 000/mm^3, serum bilirubin ≥1.5× the institutional upper limit of normal, aspartate aminotransferase and alanine aminotransferase ≤100 IU/l, and creatinine clearance ≥40 ml/min. Ejection fraction ≥60% by echocardiogram and PaO_2 ≥60 torr were also required. Patients with symptomatic brain metastasis or severe comorbidity were excluded. Each hospital's institutional review board approved the study, and written informed consent was obtained from all enrolled patients.

treatment schedule

Amrubicin was diluted in 20 ml of normal saline and administered as a bolus during a drip infusion of normal saline on days 1–3 of each treatment cycle. Carboplatin was diluted in 250 ml of 5% glucose solution and administered after amrubicin by 1-h i.v. infusion on day 1. The treatment schedule was repeated on a 21-day cycle. Premedication with corticosteroid and antiemetic 5-HT_3 antagonist was recommended. No prophylactic granulocyte colony-stimulating factor (G-CSF) or prophylactic antibiotic support was planned. G-CSF support was recommended in cases of neutrophil count decrease <1000/mm^3 or febrile neutropenia. All patients received at least three cycles of treatment unless their disease progressed, unacceptable toxicity occurred, the patient refused further treatment, or the physician decided to discontinue the treatment. Second-line chemotherapy or other treatments after disease progression were not prohibited by the protocol.

The study permitted the enrollment of patients with limited disease (LD)-SCLC as well as ED-SCLC because concurrent chemoradiotherapy was not a standard of care for elderly SCLC patients. LD-SCLC patients who were medically feasible for irradiation were recommended to receive sequential thoracic radiotherapy (total 50–60 Gy in 25–30 fractions) after three to four cycles of the protocol treatment.

The starting doses were 35 mg/m^2 of amrubicin and AUC 4.0 of carboplatin according to the result of previous phase I study [10]. When severe toxic effects such as grade 3 or more non-hematological toxic effects except nausea/vomiting, thrombocytopenia <20 000/mm^3, grade 4 neutropenia lasting ≥4 days, or febrile neutropenia occurred, the dose of amrubicin was reduced to 30 mg/m^2 in subsequent cycles.

treatment assessment

Baseline assessment included a physical examination, complete blood counts (CBC) with differential and platelet count, hepatic and renal function tests, urine analysis, 12-lead electrocardiogram, echocardiogram, and chest X-ray. Measurement of visible and palpable tumors was carried out in the baseline assessment by chest X-ray, computed tomography (CT) scans, or magnetic resonance imaging (MRI) scans (when clinically indicated). During the study, the medical history and results of physical examination, weight, vital signs, ECOG PS, CBC, and blood chemistry were monitored weekly, and urinalysis was carried out every 3 weeks. Radiographic evaluation (CT, MRI, or chest X-ray) by extramural review was carried out to assess the response to the treatment. Unidirectional measurements were undertaken using the RECIST criteria. Tumor response assessment was carried out at least every two cycles while the patients were in the study. For the confirmation of response according to the RECIST criteria, a response >4 weeks duration was needed for a complete response (CR) or partial response (PR) and >6 weeks from the initiation of chemotherapy was needed to determine the disease as stable. Toxic effects were assessed according to National Cancer Institute—Common Toxicity Criteria version 3.0.

statistical analysis

The primary end point of this study was an ORR defined as the proportion of the patients whose best response was CR or PR among all per-protocol patients. Simon's two-stage minimax design was used to determine the sample size and interim decision criteria. Assuming that an ORR of 60% in eligible patients would indicate potential usefulness, whereas an ORR of 40% would be the lower limit of interest, with $\alpha = 0.10$ and $\beta = 0.20$, the estimated accrual number was 30 patients. Secondary end points of this study were progression-free survival (PFS), overall survival, and toxicity profiles. Survival estimation was carried out using the Kaplan–Meier method. Patients alive without disease progression at the data cut-off point (December 2008) were censored at the last point when the patients were assessed to be progression free.

results

patient characteristics and treatment administration

From January 2005 to November 2007, 36 patients were enrolled from 11 institutions. The patients' characteristics are listed in Table 1. Fifty-eight percent (21 of 36) of the patients were ≥75 years. The median number of treatment cycles was 4 (range 2–7 cycles) and 89% (32 of 36) of patients could receive three cycles or more. All patients were assessable for toxicity, tumor response, and survival. Fifteen patients with LD were enrolled and 10 patients (67%) received thoracic radiotherapy after the protocol treatment. For these 10 patients, all response evaluations were confirmed before the initiation of radiotherapy. The other five patients with LD did not receive thoracic irradiation because of the following reasons: one was

Table 1. Patient characteristics

Enrolled patients	36
Gender	
Male	27
Female	9
Age	
Median	76
Range	70–83
ECOG Performance status	
0	17
1	19
Clinical stage	
Limited disease	15
Extensive disease	21

due to pericardial effusion, two were considered intolerable to radiation by radiation oncologists because of too large irradiation fields, and two were considered intolerable to radiation by attending physicians. Twenty-one patients (62%) received second-line chemotherapy after disease progression, in which the objective response was achieved in eight patients.

response and survival

The numbers of objective responses were as follows: CR 1, PR 31, stable disease (less than a 30% reduction and less than a 20% increase in the sum of the products of one longest diameters of pre-defined measurable lesions and the appearances of no new lesions) 2, and progressive disease 2 (Table 2). The ORR was 89% [95% confidence interval (CI) 79–99]. The final survival assessment was carried out in December 2008 (>1 year after the last patient enrollment). The median PFS was 5.8 months (95% CI 5.1–6.2) and MST was 18.6 months (95% CI 16.1–19.4) (Figure 1). One-year survival rate was 67%. MST of 21 patients with ED was 12.8 months (range 2.6–37.6) and that of 15 patients with LD was 18.6 months (range 8.6–30.1).

toxicity

Regarding the hematological toxic effects, 97% of patients experienced grade 3 or more neutropenia and febrile neutropenia was observed in 17% of patients. Twenty-two patients (61%) were treated with G-CSF for 2–10 days during their first treatment cycle due to neutropenia and 11 patients (31%) needed dose reduction in subsequent cycles. Although one patient suffered from sepsis after severe neutropenia, she recovered and serious complications were not observed in any other patients (Table 3). Four patients experienced grade 4 thrombocytopenia and two needed platelet transfusion, although no serious hemorrhagic event was observed. Two patients experienced grade 4 anemia and one received a blood transfusion.

The common non-hematological adverse events were nausea, infection, fatigue, diarrhea, and stomatitis, most of which were mild or moderate and recovered within a short period (Table 3). Ten patients who received thoracic radiation after this study did not experience any radiation recall phenomenon.

Table 2. Response

	No. of patients	%	95% CI
Response			
Complete response	1	3	
Partial response	31	86	
Stable disease	2	6	
Progressive disease	2	6	
Overall response rate	32	89	79–99
Disease control rate	34	94	86–100

CI, confidence interval.

discussion

The prospective studies for elderly patients with SCLC have been very limited. Since most of those studies consisted of heterogeneous populations such as elderly patients with good PS and younger patients with poor PS, their treatment outcomes varied from report to report [11]. Recently, elderly patients with good PS and normal organ functions tend to be treated with similar regimens to those of younger patients, but some reports indicated that even with good PS and normal organ functions, elderly patients had a higher risk of severe toxic effects than younger patients [12–14]. Although the carboplatin and etoposide combination has become one of the standard chemotherapies for elderly SCLC according to JCOG 9702 [7], the ORR (73%) and MST (10.6 months) of this regimen were inferior to those of the standard chemotherapy for younger SCLC patients (ORR 87% and MST 12.8 months by cisplatin and irinotecan) [15]. In this context, a prospective study to investigate a more effective regimen for elderly SCLC patients is still warranted.

In the current study, a new regimen of amrubicin combined with carboplatin achieved high efficacy (ORR of 89%, MST of 18.6 months) for elderly SCLC patients and met its primary statistical end point. Even in patients with ED, more than half of the patients could live >1 year, which is quite a better result compared with previous reports. Since the sample size of this study was too small to draw any valid conclusion, further investigation of this regimen in larger comparative study (e.g. current regimen versus carboplatin plus etoposide) is warranted.

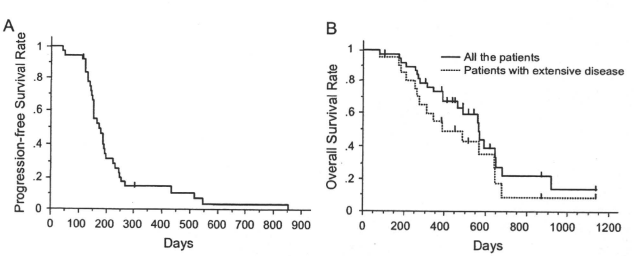


Figure 1. (A) Progression-free survival and (B) overall survival.

Table 3. Toxicity

Toxicity	No. of patients			
	Grade 2	Grade 3	Grade 4	>Grade 3 (%)
Hematological				
Neutropenia	1	9	26	35 (97)
Anemia	17	8	2	10 (28)
Thrombocytopenia	7	6	4	10 (28)
Febrile neutropenia	–	5	1	6 (17)
Non-hematological				
Infection	5	5	0	5 (14)
Nausea/vomiting	10	4	0	4 (11)
Fatigue	3	1	0	1 (3)
Diarrhea	4	0	0	0
Stomatitis	4	0	0	0
Fever	2	0	0	0
Pneumonitis	1	0	0	0
Phlebitis	1	0	0	0
Hiccup	1	0	0	0
Others[a]	1	2	0	2 (5)

[a]Includes one grade 2 depression, one grade 3 abdominal pain, and one grade 3 duodenal ulcer.

The dosage of carboplatin (AUC 4.0) in this study is lower than that used in other studies [6, 7]; however, recent large comparative studies also used carboplatin with AUC of 4.0 even for younger SCLC patients [16]. The hematological toxic effects described below as well as the efficacy observed in this study also support its appropriateness. Regarding the eligibility criteria, the current study permitted an enrollment of LD-SCLC patients, which is a different patient population from that with ED in terms of survival. Because concurrent thoracic irradiation is not a standard of care for elderly SCLC patients with LD, we considered that chemotherapy followed by radiotherapy was a proper strategy for such patients and tumor response, a primary end point of this study, could be assessable for those patients. So far, this regimen is incompatible with concurrent chemoradiation because there has been no safety data of amrubicin under the concurrent irradiation.

The principal toxicity of the amrubicin and carboplatin combination was myelosuppression, which is a similar profile to the results of previous studies of amrubicin alone, standard carboplatin plus etoposide, or our previous phase I study [7, 8, 10]. The percentage of patients with grade 3 or 4 neutropenia and that of patients who required G-CSF support in this study (97% and 61%, respectively) were also similar to those observed in carboplatin plus etoposide group in the study of Okamoto et al. (>95% and 74%, respectively) [7]. Although one patient experienced sepsis after severe neutropenia, there was no treatment-related death in this study and non-hematological toxic effects were mostly mild to moderate and reversible. Thus, we think the risk–benefit balance of this regimen is preferable for the elderly population. Despite that amrubicin is classified as anthracycline, myocardial toxicity has not been reported in previous clinical trials as well as in the current trial. Recall phenomenon, a unique toxicity related with anthracyclines, was also not observed in patients with LD treated with thoracic irradiation after this regimen. Of course, since our small study could not confirm the safety of the regimen, continuous attention should be paid especially to these rare toxic effects.

In conclusion, amrubicin combined with carboplatin is quite effective for SCLC with acceptable toxic effects even for the elderly population. Further evaluation of this regimen is warranted.

disclosure

The authors indicated no potential conflicts of interest.

references

1. Jemal A, Siegel R, Ward E et al. Cancer statistics, 2008. CA Cancer J Clin 2008; 58: 71–96.
2. Greenlee RT, Murray T, Bolden S et al. Cancer statistics, 2000. CA Cancer J Clin 2000; 50: 7–33.
3. Murren J, Glatstein E, Pass HI. Small cell lung cancer. In DeVita VT Jr, Hellman S, Rosenberg SA (eds), Cancer: Principles and Practice of Oncology, 6th edition. Philadelphia, PA: Lippincott Williams and Wilkins 2001; 983–1018.
4. Stephens RJ, Johnson DH. Treatment and outcomes for elderly patients with small cell lung cancer. Drugs Aging 2000; 17: 229–247.
5. Shepherd FA, Bezjak A. Treatment of small cell lung cancer in the elderly patients. In Pass HI, Mitchell JB, Johnson DH et al. (eds), Lung Cancer: Principles and Practice, 2nd edition. Philadelphia, PA: Lippincott Williams and Wilkins 2000; 1081–1091.
6. Okamoto H, Watanabe K, Nishiwaki Y et al. Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. J Clin Oncol 1999; 17: 3540–3545.
7. Okamoto H, Watanabe K, Kunikane H et al. Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. Br J Cancer 2007; 97: 162–169.
8. Yana T, Negoro S, Takada M et al. Phase II study of amrubicin in previously untreated patients with extensive-disease small cell lung cancer: West Japan Thoracic Oncology Group (WJTOG) study. Invest New Drugs 2007; 25: 253–258.
9. Ohe Y, Negoro S, Matsui K et al. Phase I-II study of amrubicin and cisplatin in previously untreated patients with extensive-stage small-cell lung cancer. Ann Oncol 2005; 16: 430–436.
10. Inoue A, Yamazaki K, Maemondo M et al. A phase I study of amrubicin combined with carboplatin for elderly patients with small-cell lung cancer. J Thorac Oncol 2006; 1: 551–555.
11. Sekine I, Yamamoto N, Kunitoh H et al. Treatment of small cell lung cancer in the elderly based on a critical literature review of clinical trials. Cancer Treat Rev 2004; 30: 359–368.
12. Jara C, Gómez-Aldaravi JL, Tirado R et al. Small-cell lung cancer in the elderly—is age of patient a relevant factor? Acta Oncol 1999; 38: 781–786.
13. Langer C, Manola J, Bernardo P et al. Advanced age alone does not compromise outcome in fit non-small cell lung cancer (NSCLC) patients (Pts) receiving platinum (DDP)-based therapy (TX): implications of ECOG 5592. Proc Am Soc Clin Oncol 2000; 19: (Abstr 1912).
14. Oshita F, Kurata T, Kasai T et al. Prospective evaluation of the feasibility of cisplatin-based chemotherapy for elderly lung cancer patients with normal organ functions. Jpn J Cancer Res 1995; 86: 1198–1202.
15. Noda K, Nishiwaki Y, Kawahara M et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 2002; 346: 85–91.
16. Hermes A, Bergman B, Bremnes R et al. Irinotecan plus carboplatin versus oral etoposide plus carboplatin in extensive small-cell lung cancer: a randomized phase III trial. J Clin Oncol 2008; 26: 4261–4267.