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Effectiveness of Gefitinib against Non–Small-Cell Lung Cancer with the Uncommon EGFR Mutations G719X and L861Q

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Introduction: In non–small-cell lung cancer, an exon 19 deletion and an L858R point mutation in the epidermal growth factor receptor (EGFR) are predictors of a response to EGFR-tyrosine kinase inhibitors. However, it is uncertain whether other uncommon EGFR mutations are associated with sensitivity to EGFR-tyrosine kinase inhibitors.

Methods: A post-hoc analysis to assess prognostic factors was performed with the use of patients with EGFR mutations (exon 19 deletion, L858R, G719X, and L861Q) who were treated with gefitinib in the NEJ002 study, which compared gefitinib with carboplatin-paclitaxel as the first-line therapy.

Results: In the NEJ002 study, 225 patients with EGFR mutations received gefitinib at any treatment line. The Cox proportional hazards model indicated that performance status, response to chemotherapy, response to gefitinib, and mutation types were significant prognostic factors. Overall survival (OS) was significantly shorter among patients with uncommon EGFR mutations (G719X or L861Q) compared with OS of those with common EGFR mutations (12 versus 28.4 months; $p = 0.002$). In the gefitinib group (n = 114), patients with uncommon EGFR mutations had a significantly shorter OS (11.9 versus 29.3 months; $p < 0.001$). By contrast, OS was similar between patients with uncommon mutations and those with common mutations in the carboplatin-paclitaxel group (n = 111; 22.8 versus 28 months; $p = 0.358$).

Conclusions: The post-hoc analyses clearly demonstrated shorter survival for gefitinib-treated patients with uncommon EGFR mutations compared with the survival of those with common mutations and suggest that the first-line chemotherapy may be relatively effective for non–small-cell lung cancer with uncommon EGFR mutations.

Key Words: Gefitinib, G719X, L861Q, NEJ002, Uncommon epidermal growth factor receptor mutations.

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The clinical efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib and erlotinib, has been demonstrated in non–small-cell lung cancer (NSCLC) patients in whom standard chemotherapy has failed.[1,2] Further studies have revealed that the presence of activating mutations in the EGFR kinase domain is strongly associated with the therapeutic efficacy of EGFR-TKIs.[3,4]

Randomized phase 3 trials have demonstrated that EGFR-TKIs significantly improve median progression-free survival (PFS) compared with platinum-doublet therapy in EGFR-mutated patients.[5–8] However, not all mutations in the EGFR kinase domain are responsive to EGFR-TKI treatment. These phase 3 trials have shown that EGFR-TKIs are effective for patients with common EGFR mutations, such as an exon 19 deletion or the L858R point mutation, which account for more than 90% of EGFR mutations. Retrospective studies and case reports suggest that some uncommon mutations are associated with sensitivity to EGFR-TKIs.[9–20] These mutations

include G719X in exon 18, which accounts for approximately 3% of EGFR mutations, and L861Q in exon 21, which represents approximately 2% of EGFR mutations. However, these uncommon EGFR mutations have not been clearly shown to be predictive markers for the efficacy of EGFR-TKIs because of their low frequency.

To investigate the efficacy of gefitinib in patients with uncommon mutations, we conducted a post-hoc analysis of the NEJ002, which compared gefitinib and carboplatin-paclitaxel as first-line therapies for advanced NSCLC with activating EGFR mutations.

PATIENTS AND METHODS

Patient Population

We retrospectively analyzed the data of 225 patients who received gefitinib treatment at any point in the NEJ002 study.[6] The eligibility criteria of the NEJ002 study included the presence of advanced NSCLC harboring an EGFR mutation (exon 19 deletion or L858R, G719X, or L861Q point mutation) without the resistant EGFR mutation T790M (identified using the peptide nucleic acid–locked nucleic acid polymerase chain reaction clamp method), no history of chemotherapy, an age of 75 years or younger, a performance status of 0 to 1, and appropriate organ function.[21,22] Patients provided a written informed consent. The study was conducted in accordance with the Helsinki Declaration of the World Medical Association. The protocol was approved by the institutional review board of each participating institution.

Treatment

Eligible patients were randomly assigned to receive either gefitinib (250 mg/day) or paclitaxel (200 mg/m^2)/carboplatin (area under the curve, 6.0) on day 1 every 3 weeks. Chemotherapy was continued for at least three cycles. Gefitinib was administered until the disease progressed, intolerable toxicities developed, or consent was withdrawn. The protocol recommended that the crossover regimen be used as a second-line treatment.

Clinical Assessments

The antitumor response to treatment was assessed using computed tomography every 2 months. Unidirectional measurements were adopted on the basis of the Response Evaluation Criteria in Solid Tumors (version 1.0).[23] PFS was evaluated from the date of randomization to the date when disease progression was first observed or death occurred. The treatment response and PFS were determined by an external review of computed tomography scans by experts who were not aware of the treatment assignments. Overall survival (OS) was evaluated from the date of randomization to the date of death.

Statistical Analysis

To assess prognostic factors for OS, we used univariate and multivariate Cox proportional hazards models. Kaplan–Meier survival curves were constructed for PFS and OS, and differences between groups were identified using the log-rank test. Differences in response rates were identified using Fisher's exact test. Each analysis was two sided, with a 5% significance level and a 95% confidence interval. All analyses were performed using SAS for Windows software (release 9.1; SAS Institute, Cary, NC).

RESULTS

Patient Population

A total of 230 chemonaive patients were enrolled in the NEJ002 study: 115 patients were assigned to receive gefitinib and 115 were assigned to receive carboplatin-paclitaxel (Fig. 1). To evaluate the efficacy of gefitinib in NSCLC patients with uncommon EGFR mutations, we analyzed the data of 114 patients in the gefitinib group and 111 patients in the carboplatin-paclitaxel group. We identified five patients who had uncommon EGFR mutations in each group. Two patients, who had common mutations and were treated with first-line chemotherapy consisting of carboplatin-paclitaxel, were excluded from the PFS analysis in the NEJ002 study. However, both were treated with gefitinib and were included in this post-hoc analysis. The demographic and disease characteristics of the patients with uncommon EGFR mutations were similar to those of patients with common EGFR mutations (Table 1). The characteristics of each patient with uncommon EGFR mutations are shown in supplementary Table S1 (Supplemental Digital Content 1, http://links.lww.com/JTO/A494).

Survival Factors

In the univariate analysis of 225 patients who received gefitinib at any point, uncommon EGFR mutations had a significant detrimental effect on survival (Table 2). We also identified performance statuses 1 and 2, distant metastasis, brain metastasis, stable disease, and progressive disease as significant predictors of worse prognosis for standard chemotherapy and stable disease and progressive disease as significant predictors of worse prognosis for gefitinib. When these variables were included in the Cox proportional hazards model, we found that uncommon EGFR mutations, performance statuses 1 and 2, stable disease and progressive disease for standard chemotherapy, and stable disease and progressive disease for gefitinib had significant hazard ratios (Table 2).

Uncommon EGFR Mutations and Survival

The Kaplan–Meier curve for OS for uncommon versus common EGFR mutations is shown in Figure 2A. The OS was significantly shorter among patients with uncommon EGFR mutations compared with OS of those with common EGFR mutations in the overall population (12 versus 28.4 months; p = 0.002). A significantly shorter survival time was observed in patients with uncommon EGFR mutations compared with survival time in those with common EGFR mutations in the gefitinib group (11.9 versus 29.3 months; p < 0.001) (Fig. 2B). However, a similar survival time was observed between the subgroups of uncommon and common EGFR mutations in the carboplatin-paclitaxel group (22.8 versus 28 months; p = 0.358) (Fig. 2C).
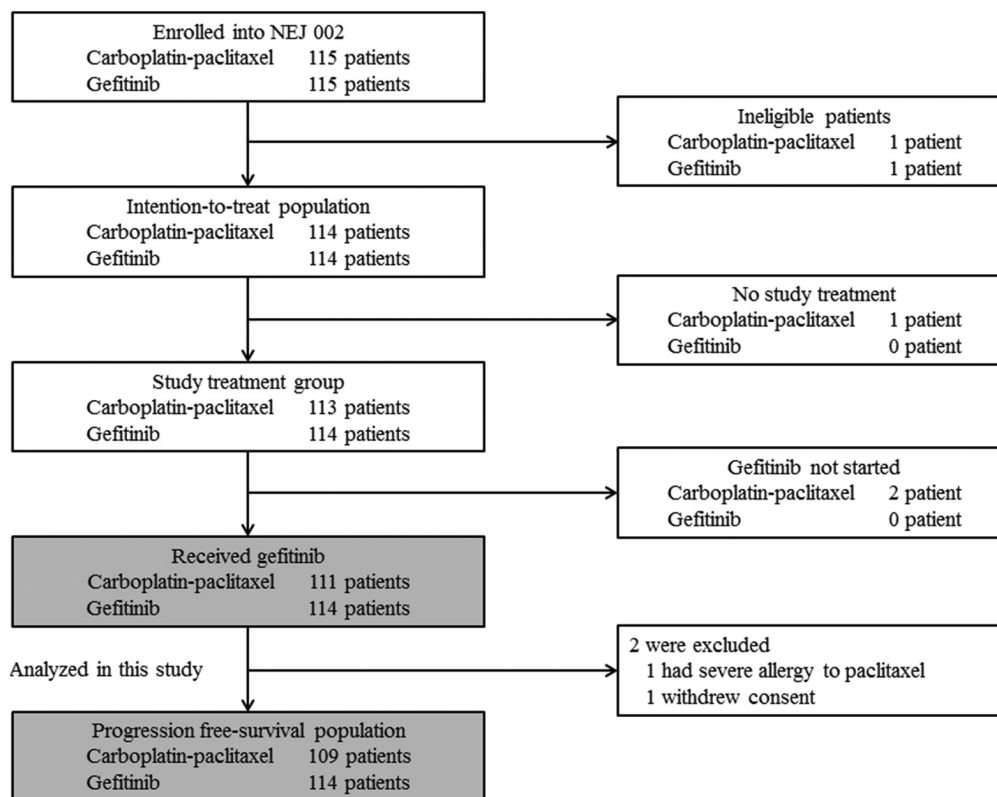
FIGURE 1. Enrollment, randomization, and follow-up of the study patients.

To examine whether the sequence of platinum doublet and gefitinib affected OS, we performed a further subgroup analysis. The survival time tended to be shorter among patients receiving first-line gefitinib compared with the survival time among those receiving first-line carboplatin-paclitaxel in the uncommon EGFR mutation group (11.9 versus 22.8 months; $p = 0.102$). Consistent with previous publications, a similar survival time was observed between patients receiving first-line gefitinib and those receiving first-line carboplatin-paclitaxel in the common EGFR mutation group (29.3 versus 28 months; $p = 0.378$).

Uncommon EGFR Mutations, PFS, and Response

In the gefitinib group, the median PFS was significantly shorter for patients with uncommon EGFR mutations compared with median PFS of those with common EGFR mutations (2.2 versus 11.4 months; $p < 0.001$) (Fig. 3*A*). By contrast, the median PFS did not differ significantly between patients with uncommon EGFR mutations and those with common EGFR mutations in the carboplatin-paclitaxel group (5.9 versus 5.4 months; $p = 0.847$) (Fig. 3*B*). The objective response rate was significantly lower in patients with uncommon EGFR mutations compared with the objective response rate in those with common EGFR mutations when treated with gefitinib (20% versus 76%; $p = 0.017$) (supplementary Table S2, Supplemental Digital Content 1, http://links.lww.com/JTO/A494). By contrast, similar objective response rates were observed for patients with uncommon EGFR mutations and those with common EGFR mutations in the carboplatin-paclitaxel group (20% versus 32%; $p = 0.336$) (supplementary Table S2, Supplemental Digital Content 1, http://links.lww.com/JTO/A494).

DISCUSSION

Recent studies suggest that NSCLC patients with uncommon EGFR mutations are less responsive to EGFR-TKIs compared with patients with L858R and exon 19 deletions.[9–20] However, the efficacy of EGFR-TKIs in NSCLC patients with uncommon mutations has not been fully elucidated.

We conducted a post-hoc analysis of the NEJ002 study to evaluate the effectiveness of gefitinib against NSCLC with G719X or L861Q. The NEJ002 study, comparing gefitinib and standard carboplatin-paclitaxel chemotherapy as the first-line treatment for patients with EGFR mutations, demonstrated no significant difference in OS between gefitinib and carboplatin-paclitaxel.[6] In contrast to other phase 3 trials investigating EGFR-TKIs for patients with common EGFR mutations of exon 19 deletion and L858R, the NEJ002 is the only study that included uncommon EGFR mutations of G719X and L861Q.

The current study clearly demonstrated that NSCLC patients with the uncommon EGFR mutations G719X and L861Q had shorter survival than the survival of those with an exon 19 deletion or L858R mutation (Fig. 2). Our results are consistent with other clinical studies on EGFR-TKIs in

TABLE 1. Patient Characteristics

Number of Patients	Uncommon Mutation 10	Common Mutation 215
Sex		
Female	4	139
Male	6	76
Age (yr)		
Median	63	65
Range	42–75	35–75
Smoking status		
Never smoked	5	134
Smoker	5	81
Performance status		
0/1/2	5/5/0	105/107/3
Histology		
Adenocarcinoma	9	202
Others	1	13
Clinical stage		
Stage IIIB	3	32
Stage IV	6	165
Postoperative	1	18
Type of EGFR mutation		
G719X	7	
L861Q	3	
Exon 19 deletion		115
L858R		97
19 deletion + L858R		3

EGFR, epidermal growth factor receptor.

G719A. To investigate the effectiveness of gefitinib on each uncommon EGFR mutations, we evaluated the difference in OS between patients with uncommon EGFR mutations (G719C versus G719S and G719X versus L861Q). There was no significant difference between these subgroups (data not shown).

This study showed that the PFS and OS tended to be shorter among patients treated with first-line gefitinib compared with PFS and OS among those treated with first-line carboplatin-paclitaxel in the uncommon EGFR mutation group (supplementary Table S2, Supplemental Digital Content 1, http://links.lww.com/JTO/A494). We also found poor disease control rate with gefitinib in patients with uncommon mutations. Three of five patients with uncommon mutations in the gefitinib group had progressive disease. By contrast, no patients with uncommon mutations had progressive disease in the carboplatin-paclitaxel group. Although the number of patients with uncommon mutations in each treatment group was small, platinum-doublet therapy might be a better choice than gefitinib for first-line therapy in patients with uncommon EGFR mutations. Because some of patients with uncommon mutations showed good clinical response to gefitinib in this study and they seemed to be heterogeneous in terms of response to gefitinib, administration of gefitinib should be considered for patients with uncommon mutations when disease progression was observed after first-line chemotherapy.

In vitro studies have indicated that the affinity of gefitinib for EGFR proteins with uncommon EGFR mutations is lower than the affinity of gefitinib for EGFR proteins with common EGFR mutations.[25] A sixfold or 14-fold higher concentration of gefitinib was required to inhibit the growth of cells expressing G719X or L861Q, respectively, compared with cells expressing L858R.[26] These results may explain the lack of response to gefitinib in patients with uncommon EGFR mutations. The authors also examined the sensitivity of G719X and L861Q mutations to erlotinib and irreversible TKIs.[27] Cells expressing G719X were less resistant to erlotinib than gefitinib in vitro; however, L861Q was resistant to both erlotinib and gefitinib. In contrast to erlotinib, irreversible TKIs inhibited the growth of cells with G719X or L861Q at a

patients with uncommon EGFR mutations (supplementary Table S3, Supplemental Digital Content 1, http://links.lww.com/JTO/A494). The overall response rate to EGFR-TKIs in patients with uncommon EGFR mutations was 41%, which is lower than the response rate to TKIs (62%–83%) of patients with common EGFR mutations.[7,8,24] In the NEJ002 study, G719X included G719C and G719S. No patients harbored

TABLE 2. Univariate and Multivariate Analysis by Cox Proportional Hazards Model

	Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*
Age (≥70/<70)	1.047	0.719–1.525	0.81			
Sex (female/male)	0.73	0.51–1.045	0.86			
Smoking status (+/−)	1.376	0.967–1.958	0.076			
Performance status (1, 2/0)	1.792	1.263–2.541	0.001	1.85	1.297–2.639	0.001
Histology (nonadeno/adeno)	0.647	0.302–1.387	0.263			
Types of EGFR-m (uncommon/common)	2.967	1.501–5.868	0.018	2.445	1.177–5.079	0.017
Distant metastasis (+/−)	4.914	1.113–5.741	0.027	2.849	1.241–6.54	0.135
Brain metastasis (+/−)	1.781	1.248–2.542	0.002	1.311	0.897–1.915	0.162
Response to Cb/TXL (SD, PD/CR, PR)	1.742	1.113–2.728	0.015	1.748	1.11–2.754	0.016
Response to G (SD, PD/CR, PR)	2.878	2.012–4.117	0.002	2.601	1.794–3.771	<0.001

HR, hazard ratio; CI, confidential interval; EGFR-m, epidermal growth factor receptor mutation; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; Cb/TXL, carboplatin plus paclitaxel; G, gefitinib.
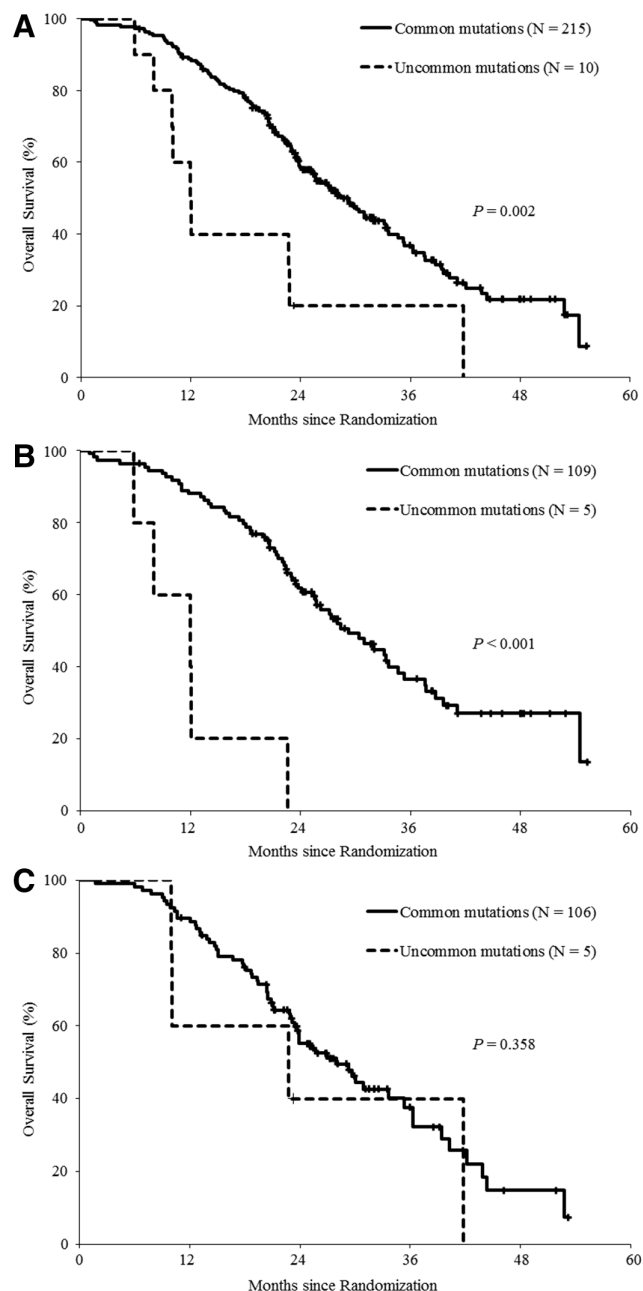
FIGURE 2. The overall survival curves of patients with common mutations and uncommon mutations in the entire population (*A*), the gefitinib group (*B*), and the carboplatin-paclitaxel group (*C*).

FIGURE 3. Progression-free survival curves in the gefitinib group (*A*) and the carboplatin-paclitaxel group (*B*) according to the type of epidermal growth factor receptor mutation.

lower concentration than those with wild-type EGFR. Indeed, Sequist et al.[28] reported that the effectiveness of an irreversible pan-ErbB receptor TKI, neratinib, on NSCLC patients with G719X. Niratinib induced partial responses in three of four patients with G719X and the fourth had durable stable disease for 40 weeks. It may be beneficial to evaluate erlotinib as a treatment for NSCLCs with G719X and irreversible EGFR-TKIs as treatments for NSCLCs with G719X and L861Q. Because previous pha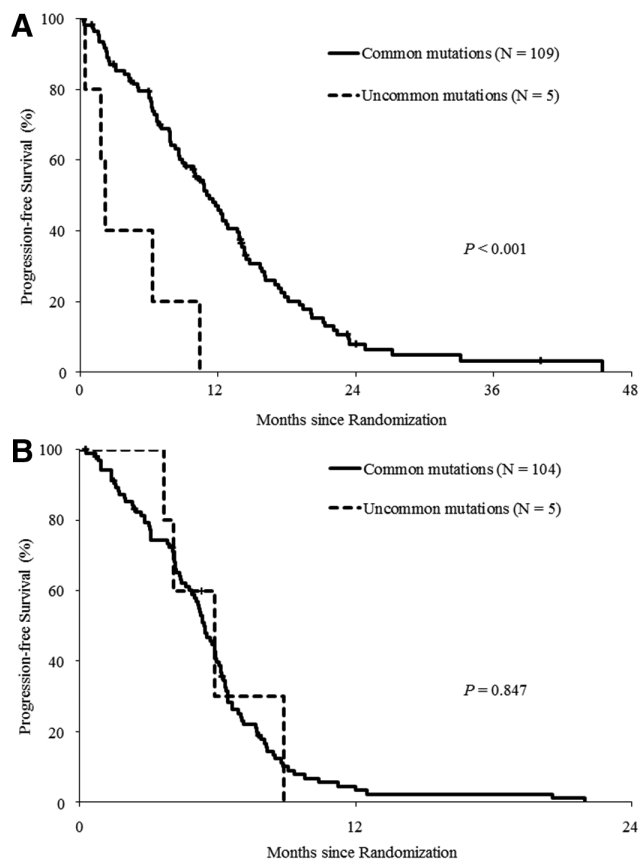se 3 trials that investigated erlotinib or irreversible TKIs for NSCLC with EGFR mutations did not include uncommon EGFR mutations, further clinical studies may need to be performed.[7,8,29]

Another possible strategy for the treatment of uncommon EGFR mutations is the combination of EGFR-TKIs and cytotoxic agents. Our group has undertaken a randomized phase 3 trial to compare gefitinib plus carboplatin plus pemetrexed with gefitinib monotherapy for patients with NSCLC with an exon 19 deletion or an L858R, G719X, or L861Q EGFR mutation (NEJ009; University Hospital Medical Information Network Clinical Trials Registry [UMIN-CTR] number, UMIN000006340). The data from this study will advance the treatment of NSCLC with uncommon EGFR mutations.

In conclusion, our post-hoc analysis clearly demonstrated shorter survival of TKI-treated patients with uncommon EGFR mutations compared with survival of those with common EGFR mutations. Furthermore, the data suggest that the first-line chemotherapy may be relatively effective for NSCLC with uncommon EGFR mutations.

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