First-Line Gefitinib in Patients Aged 75 or Older With Advanced Non–Small Cell Lung Cancer Harboring Epidermal Growth Factor Receptor Mutations

NEJ 003 Study

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Introduction: Recent studies have demonstrated that first-line treatment with gefitinib, an epidermal growth factor receptor (EFGR)–targeted tyrosine kinase inhibitor, is significantly superior to standard chemotherapy for advanced non–small-cell lung cancer (NSCLC) harboring EGFR sensitive mutations. Meanwhile, the efficacy of gefitinib therapy among elderly populations diagnosed with EGFR-mutated NSCLC has not yet been elucidated. The purpose of this study was to investigate the efficacy and feasibility of gefitinib for chemotherapy-naive patients aged 75 or older with NSCLC harboring EGFR mutations; generally, these patients have no indication for treatment with platinum doublets.

Methods: Chemotherapy-naive patients aged 75 years or older with performance status 0 to 1 and advanced NSCLC harboring EGFR mutations, as determined by the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method, were enrolled. The enrolled patients received 250 mg/day of gefitinib orally.

Results: Between January 2008 and May 2009, 31 patients were enrolled, all of whom were eligible. The median age was 80 (range, 75–87) years. Twenty-five patients (81%) were women, and 30 patients (97%) had adenocarcinoma. The overall response rate was 74% (95% confidence interval, 58%–91%), and the disease control rate was 90%. The median progression-free survival was 12.3 months. The common adverse events were rash, diarrhea, and liver dysfunction. One treatment-related death because of interstitial lung disease occurred.

Conclusions: This is the first study that verified safety and efficacy of first-line treatment with gefitinib in elderly patients having advanced NSCLC with EGFR mutation. Considering its strong antitumor activity and mild toxicity, first-line gefitinib may be preferable to standard chemotherapy for this population.

Key Words: Non–small cell lung cancer, Epidermal growth factor receptor mutation, Gefitinib

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Non–small-cell lung cancer (NSCLC), which accounts for 80% of lung cancer, remains the major cause of cancer-related death in both Western and Asian countries. With prolongation of life expectancy, both the incidence and mortality of lung cancer in the elderly are rising. In Japan, 48 500 individuals aged 70 years or older were estimated to die of lung cancer in 2009[1]; moreover, the ratio of elderly patients dying from lung cancer increased from 57% in 1989 to 72% in 2009. Treatment strategy in elderly patients with lung cancer has, thus, become an important issue.

About half of the newly diagnosed NSCLC patients have advanced disease, with no indication for local therapy such as surgery and radiotherapy. Chemotherapy for the elderly shows similar efficacy to that observed in younger

patients. However, it is generally more toxic, in terms of both incidence and severity, because of age-related weakening of organ function.[2] Consequently, standard chemotherapy for elderly NSCLC patients, especially those aged 75 years or older, is performed as monotherapy with vinorelbine, gemcitabine, or docetaxel instead of platinum doublets, which are the standard for younger patients.[3–7] Although a recent phase III study suggested that the platinum doublet of monthly carboplatin and weekly paclitaxel may be superior to the gemcitabine or vinorelbine monotherapy in the elderly population, the treatment-related death rate of the doublet group was determined to be 7%.[8] Thus, investigation into safer and more effective treatments for elderly NSCLC patients is required.

Gefitinib, an orally administered tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR), is a key molecularly targeted drug used for the treatment of advanced NSCLC. In May 2004, seminal studies showed that the presence of somatic mutations in the kinase domain of EGFR strongly correlated with increased responsiveness to EGFR TKIs in patients with NSCLC.[9,10] Before this observation, it had been known that subgroups of NSCLC patients, including those of Asian race, female sex, nonsmoking status, and having adenocarcinoma, displayed significant responses to gefitinib.[11,12] These subgroups turned out to have a high incidence of EGFR mutations.[13] Recently, two phase III studies comparing gefitinib treatment with chemotherapy in chemo-naive patients selected on the basis of EGFR mutations were reported from Japan.[14,15] These studies revealed the superiority of gefitinib treatment over standard chemotherapy by demonstrating that first-line gefitinib administration doubled progression-free survival (PFS) as compared with standard chemotherapy. One of two studies we conducted, namely the NEJ002 study, demonstrated that treatment with gefitinib provided patients with a better quality of life as compared with chemotherapy.[16] The eligibility criteria in these studies was limited to patients aged 75 years or younger, as the treatments with platinum doublets were considered to be inappropriate for more elderly populations because of increased toxicity. Moreover, it has been reported in Japan that this more elderly group of patients develop interstitial lung disease (ILD) frequently when treated with gefitinib.[17] In previous studies, we demonstrated that patient selection by EGFR mutation can dramatically improve the risk–benefit balance of gefitinib treatment; however, no study thus far has investigated the efficacy and feasibility of first-line gefitinib treatment in elderly NSCLC patients with EGFR mutation. Thus, the current phase II study was conducted.

METHODS

Patient Selection

This multicentric phase II study was approved by the institutional review board of each participating institute. The main eligibility criterion was to select chemotherapy-naive patients with NSCLC harboring sensitive EGFR mutations. Namely, patients with exon 19 deletions, L858R, L861Q, G719A, or G719S were included, but those with a resistant T790M mutation were excluded. Patients who were 75 years of age or older with Eastern Cooperative Oncology Group performance status (PS) 0 to 2 were also deemed eligible. Other eligibility requirements were stage IIIB to IV or postoperative recurrent NSCLC, presence of a measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST), adequate organ function including liver function (aspartate transaminase and alanine aminotransferase ≤100 U/liter, total bilirubin <2.0 mg/dL), and written informed consent.

EGFR Mutation

Cytological or histological specimens were examined for EGFR mutation by the peptide nucleic acid-locked nucleic acid polymerase chain reaction (PCR) clamp method.[18] Briefly, genomic DNA fragments containing mutation hot spots of the EGFR gene were amplified via PCR in the presence of a peptide nucleic acid clamp primer synthesized from a peptide nucleic acid with a wild-type sequence. This method leads to preferential amplification of the mutant sequence, which is then detected by a fluorescent primer that incorporates locked nucleic acids to increase the specificity. As a result, the mutant EGFR sequence is detected in specimens that contain 100 to 1000 excess copies of wild-type EGFR sequence. The sensitivity and specificity of the peptide nucleic acid-locked nucleic acid PCR clamp method are 97% and 100%, respectively.

Drug Administration

Gefitinib was administered orally once a day at a dose of 250 mg. Patients continued to receive gefitinib until progression of disease, occurrence of intolerable severe toxicity, or withdrawal of consent. When severe toxicity was observed, patients were allowed to receive a reduced dose of gefitinib in accordance with the protocol.

Treatment Assessment

Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were determined based on RECIST version 1.0. The primary end point of this study was overall objective response rate (ORR), which was the rate of patients with CR + PR; secondary end points were PFS, overall survival (OS), and toxicities. Computer

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tomography (CT) scans were taken every month until CR or PR was observed. CR and PR required confirmation via reassessment no earlier than 4 weeks after the first assessment meeting the criteria for response. After the confirmation, CT scans were taken every other month until PD was observed. The CT films of all patients were extramurally reviewed for confirmation of response. PFS was defined as the time from the date of randomization to the first observation of disease progression or death. OS was defined as the time from the date of randomization to the date of death or the most recent follow-up. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.

Statistical Consideration

Sample size was determined using the data as follows. Response rates greater than 70% had been previously observed in nonage-restricted patients with EGFR-mutated NSCLC.[15] Meanwhile, clinical studies with elderly patients that investigated the efficacy of first-line chemotherapies in Japan showed ORR of 28% to 55%.[7,19] Thus, we assumed that an ORR of more than 55% was clinically useful, whereas an ORR of less than 30% was not clinically useful. With $\alpha = 0.05$ and $\beta = 0.1$, the number of patients required was 27. Allowing 10% loss in follow-up, a total of 30 patients were planned for enrollment.

All enrolled patients were evaluated for efficacy of received regimen. All patients treated with gefitinib, even for a short period of time, were entered into safety analysis.

RESULTS

Patient Characteristics

Between January 2008 and May 2009, a total of 31 patients were enrolled. Baseline characteristics are described in Table 1. The median age at the time of enrollment was 80.3 years (range, 75–89 years); 52% of the patients were over the age of 80. Of the 31 patients enrolled, 25 (81%) were women and 2 (6%) had a PS of 2. Histological types were all adenocarcinoma except for one adenosquamous carcinoma. There were 7 patients (23%) with stage IIIB, 22 (71%) with stage IV, and 2 (6%) with postoperative recurrence.

Efficacy

The ORR was 74.2% (95% confidence interval [CI], 57.9%–90.5%); one patient had CR, and 22 patients had PR. Five of the remaining 8 patients (16.1%) had SD, with the resulting disease control rate (CR + PR + SD) reaching 90.3% (Table 2). This result attained the primary end point by a wide margin. The median follow-up period at the time of analysis was 27.5 months. Of all 31 patients enrolled, 15 (48.3%) were alive and free from progression for at least 6 months. The median PFS was 12.1 months (Fig. 1*A*), the 1-year OS was 83.9% (95% CI, 70.2%–97.6%), and 2-year OS was 58.1% (95% CI, 45.2%–70.9%). At the data cutoff point (December 2010), 13 patients (41.9%) had died, and the median OS was 33.8 months (Fig. 1*B*).

TABLE 1. Character

	N = 31	(%)
Sex		
Women	6	19
Men	25	81
Age		
Mean (SD)	80.3	(4.1)
Range	75–89	
Smoking status		
Nonsmoker	23	74
Smoker	8	26
Performance status		
0	16	55
1	13	39
2	2	6
Stage		
IIIB	7	23
IV	22	71
Postop	2	6
Histology		
Adenocarcinoma	30	97
Adenosquamous	1	3

Safety and Toxicity

Toxicity data for all 31 patients are presented in Table 3. Nine patients (29%) had a grade 3 adverse event (AE); 1 had a grade 5 AE ILD, and died of respiratory failure. The most common hematologic AE was elevation of transaminases; grade 3 to 4 elevation occurred in three patients (19%). The most common nonhematologic AEs were rash in 21 patients (71%), diarrhea in 10 patients (32%), and appetite loss in 9 patients (29%). Dose reduction was seen in 14 patients (45%). Incidence and severity of AEs were acceptable and comparable with previous reports.[13–15]

Treatment After Progression of Disease

Patient management after the protocol treatment was retrospectively investigated. Any treatment was allowed after confirmation of PD. Gefitinib was continued in 10 of 20 patients confirmed to have PD. Three patients were treated with monotherapies of cytotoxic agents, including vinorelbine, gemcitabine, or docetaxel, and one patient was given

TABLE 2. Response Rate of Treatment With Gefitinib

Response	N = 31	(%)
CR	**1**	**3**
PR	**22**	**71**
Stable disease	**5**	**16**
Progressive disease	**3**	**10**
Overall response rate (CR + PR)	**23**	**74**
95% confidence interval		(57.9–90.5)

CR, complete response; PR, partial response.

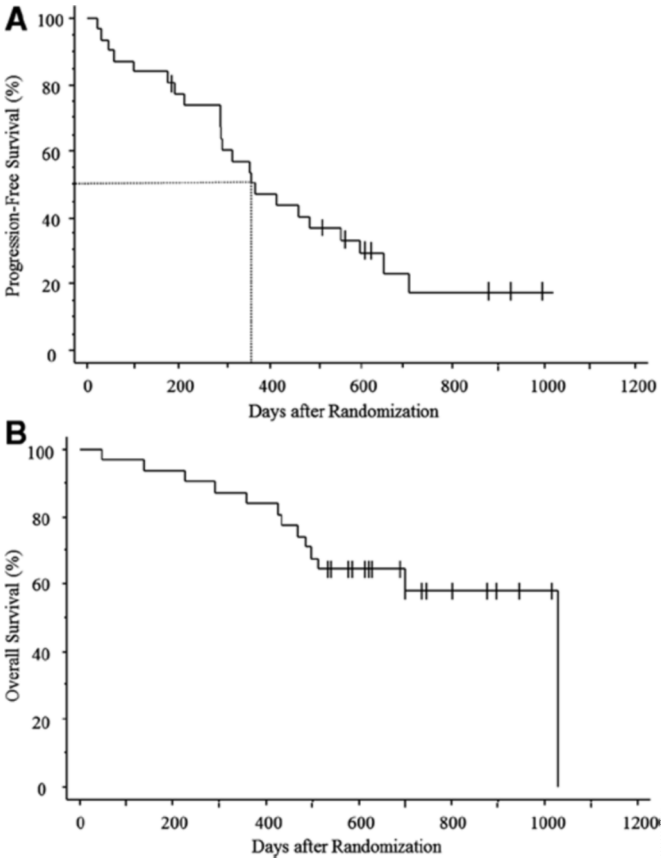

FIGURE 1. Progression-free survival and overall survival. Kaplan–Meier curves for progression-free survival are shown for the progression-free survival population (*A*), and Kaplan–Meier curves for overall survival are shown in (*B*). In (*A*) and (*B*), tick marks indicate patients for whom data were censored.

TABLE 3. Safety—Hematologic and Nonhematologic Toxicity

	NCI-CTC Grade					Grade
	1	2	3	4	5	3–4 (%)
Hematologic adverse events						
Leukocytopenia	2	1	0	0	0	0
Neutropenia	0	1	0	0	0	0
Anemia	6	4	0	0	0	0
Thrombocytopenia	2	1	0	0	0	0
AST/ALT	7	2	6	0	0	19
T-Bil	3	1	0	0	0	0
Creatinine	5	1	0	0	0	0
Hyperkalemia	7	0	0	0	0	0
Nonhematologic adverse events						
Pneumonitis	0	0	0	0	1[a]	3
Rash	12	10	1	0		3
Nail change	4	2	0	0		0
Stomatitis	3	0	0	0		0
Alopecia	3	0	0	0		0
Appetite loss	7	2	1	0		3
Nausea/vomiting	1	0	0	0		0
Diarrhea	9	2	1	0		3
Constipation	2	0	0	0		0
Fatigue	4	1	0	0		0

NCI-CTC, National Cancer Institute Common. Terminology Criteria; AST, androgen suppression therapy; ALT, alanine aminotransferase; T-Bil, total bilirubin.
[a]Treatmant-related death.

erlotinib. No patient was treated with platinum doublets. Six patients did not receive any second-line treatment.

DISCUSSION

This is the first study targeting elderly patients with EGFR-mutated NSCLC. In this study, gefitinib displayed remarkable efficacy without increased toxicity.

We have previously reported a single-arm phase II study in which gefitinib was administered to frail patients with poor PS or elderly patients who were unfit to undergo treatment with cytotoxic agents.[20] In that study, the patients enrolled were 20 to 74 years old with a PS of 3 to 4, 75 to 79 years old with a PS of 2 to 4, and aged 80 years or older (super-elderly) with a PS of 1 to 4. Patients older than 74 years of age accounted for 39% of the total enrolled patients but, nevertheless, OS was 17.8 months (Table 4). The current study strengthened the conclusion of the previous one and provided more information with respect to the efficacy of gefitinib in elderly NSCLC patients with EGFR mutation.

We defined elderly patients as those who were 75 years old and older. Many studies and subgroup analyses were performed by considering elderly cases as 70 years of age or older, especially in Western countries. We have regarded patients aged 70 to 75 years as being treatable with platinum-based chemotherapy. In fact, patients in this age group were enrolled in the NEJ002 study and were able to withstand treatment with platinum doublet. Accordingly, we excluded this group of patients from enrollment in the present study. Considering the aging of population structures and the increased longevity in Japan, we thought that the candidate selection for this study was reasonable.

Currently, in elderly patients, single-agent chemotherapy with a third generation agent (vinorelbine, gemcitabine, or taxanes) is the recommended approach according to the American Society of Clinical Oncology guidelines.[2–7] Gefitinib, which is considered minimally toxic, is often selected for the treatment of advanced NSCLC in elderly patients. Crino et al. performed a randomized phase II study (Gefitinib Versus Vinorelbine in Chemotherapy-Naïve Elderly Patients With Advanced Non-Small-Cell Lung Cancer [INVITE]) of gefitinib versus vinorelbine treatment in 196 chemotherapy-naive unselected elderly patients.[21] There were no statistical differences between gefitinib and vinorelbine in terms of PFS, OS, and ORR. Their study showed obviously lower efficacy of gefitinib in nonselected patients, as compared with the results shown from our study of EGFR-mutated patients.[22–24] These differences in effectiveness among studies highlight the importance of selection of patients by EGFR mutation analysis when administrating gefitinib. Furthermore, in another study of gefitinib treatment in Japanese patients aged

TABLE 4. Pivotal Clinical Trials of Cytotoxic Agents or EGFR-TKIs in Elder Patients With NSCLC and Recent Trials of Gefitinib in Patients selected by EGFR Mutation

Trial	Treatment	*n*	ORR (%)	PFS (mo)	MST (mo)	*p* Value
Cytotoxic agent in unselected elder patients						
ELVIS[3]	VNR	76	19.7		6.4	0.04
	BSC	78	—		4.8	
MILES[5]	VNR + GEM	232	21	4.1	6.9	NS
	GEM	233	16	4.4	6.5	
	VNR	233	18	4.4	8.3	
WJTOG9904[7]	DTX	89	22.7	5.5	14.3	$p = 0.138$
	VNR	91	9.9	3.1	9.9	
EGFR-TKI in unselected elder patients						
Ebi N.[25]	Gefitinib	49	25	4	10	—
Crino L.[21]	Gefitinib	97	3.1	2.7	5.9	NS
	VNR	99	5.1	2.9	8.0	
Jackman D. M.[27]	Erlotinib	80	10	3.5	10.9	—
Chen Y. M.[28]	Erlotinib	57	22.8	4.6	11.7	$p = 0.70$
	VNR	56	8.9	2.5	9.3	
EGFR-TKI in selected younger patients						
WJTOG3405[14]	Gefitinib	86	62.1	9.2	Immature	$p < 0.001$ (PFS)
	CDDP + DTX	86	32.2	6.3		
NEJ002[15]	Gefitinib	114	73.7	10.8	30.5	$p < 0.001$ (PFS)
	CBDCA + PTX	110	30.7	5.4	23.6	
EGFR-TKI in selected elder patients (current study)						
NEJ003	Gefitinib	31	74.2	12.1	33.8	—

ELVIS, Elderly Lung Cancer Vinorelbine Italian Study; MILES, Multicenter Italian Lung Cancer in the Elderly Study; ORR, overall response rate; PFS, progression-free survival; MST, median survival time; VNR, vinorelbine; BSC, best supportive care; NS, not significant; GEM, gemcitabine; DTX, docetaxel; EGFR-TKI, epidermal growth factor receptor–tyrosine kinase inhibitors; CDDP, cisplatin; CBDCA, carboplatin; PTX, paclitaxel.

75 or older, which included about 40% of the patients who were examined for EGFR mutations and 14% of the patients with EGFR-mutated tumors, the response rate was only 25%.[25] Meanwhile, there have been a few studies of treatment for elderly unselected patients with erlotinib, which is supposed to be more toxic than gefitinib as the administered dose was set near the maximum tolerance dose.[26,27] The response rates in these studies were 10% or less, which were similar to those from the gefitinib studies conducted in Western populations (Table 4). In the other Asian study, erlotinib was compared with vinorelbine treatment in patients aged 70 or older.[28] That study demonstrated that erlotinib yielded a higher response rate and PFS than vinorelbine. The percentage of mutation-positive patients was 30% of those who were examined for EGFR mutations in the erlotinib group. This high proportion might have contributed to the better results of the erlotinib group. The treatment of unselected NSCLC patients with erlotinib was also as ineffective as with gefitinib. Efficacy results in patients selected by EGFR mutation in the current study were substantially superior to those observed in the studies of gefitinib or erlotinib with unselected cases. Surprisingly, the median PFS and 2 year-survival rate here were comparable with results obtained in NEJ002 (12.3 versus 10.8 months, 58% versus 61%, respectively) despite the limited enrollment of an elderly population in this study. These two studies, namely NEJ002 and NEJ003, have very similar backgrounds as they were performed during almost the same time period at identical institutions. It was suggested that gefitinib displayed similar efficacy in elderly patients when compared with their younger counterparts (Table 4). Although the current phase II study could not verify whether gefitinib prolonged PFS in elderly patients in comparison with younger patients, gefitinib might still prove to be the most suitable agent for elderly patients with EGFR-mutated NSCLC.

Elderly patients generally have more comorbidities and lower organ function than younger patients. Treatment-related toxicity in the elderly is a more significant issue than for younger patients. A subgroup analysis of BR.21 showed that elderly patients treated with erlotinib displayed similar efficacy with respect to survival and quality of life as their younger counterparts but experienced greater toxicity.[27] In the current study, toxicity was generally mild and predictable. Rash, diarrhea, and elevation of transaminase were observed frequently, similar to other studies with EGFR-TKIs. The single case of treatment-related death that occurred in our study was because of ILD, although this condition was not found in other patients. The frequency of ILD in the current study was comparable with that previously reported in Japan. Unfortunately, this patient did not respond to treatment with a large dose of corticosteroid, which is generally used for such conditions.[17,29] Advanced age and smoking, preexisting ILD, and poor performance status have been reported as risk factors for ILD during treatment with gefitinib.[17] Elderly patients treated with EGFR-TKIs should be monitored with further caution for ILD. On the whole, gefitinib was found to be a well-tolerated therapy for elderly patients with mutated NSCLC.

In conclusion, first-line gefitinib treatment is highly effective with acceptable toxicity for elderly patients with advanced NSCLC harboring EGFR mutations. Together with our previous studies (NEJ001, NEJ002), gefitinib is shown to be an ideal therapy for all types of NSCLC patients with EGFR mutation.

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