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Efficacy of chemotherapy after first-line gefitinib therapy in *EGFR* mutation-positive advanced non-small cell lung cancer—data from a randomized Phase III study comparing gefitinib with carboplatin plus paclitaxel (NEJ002)

Eisaku Miyauchi[1], Akira Inoue[1,*], Kunihiko Kobayashi[2], Makoto Maemondo[3], Shunichi Sugawara[4], Satoshi Oizumi[5], Hiroshi Isobe[6], Akihiko Gemma[7], Yasuo Saijo[8], Hirohisa Yoshizawa[9], Koichi Hagiwara[10], and Toshihiro Nukiwa[11] for the North-East Japan Study Group

[1]Department of Respiratory Medicine, Tohoku University Hospital, Sendai, [2]Department of Respiratory Medicine, Saitama Medical University Internal Medical Center, Saitama, [3]Department of Respiratory Medicine, Miyagi Cancer Center, Miyagi, [4]Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, [5]First Department of Medicine, Hokkaido University School of Medicine, Sapporo, [6]Department of Medical Oncology, KKR Sapporo Medical Center, Sapporo, [7]Department of Pulmonary Medicine and Oncology, Graduate School, Nippon Medical School, Tokyo, [8]Department of Medical Oncology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, [9]Bioscience Medical Research Center, Niigata University Medical & Dental Hospital, Niigata, [10]Department of Respiratory Medicine, Saitama Medical University, Saitama, and [11]Department of Respiratory Medicine, South Miyagi Medical Center, Miyagi, Japan

*For reprints and all correspondence: Akira Inoue, Department of Respiratory Medicine, Tohoku University Hospital, 1-1, Seiryomachi, Aoba-ku, Sendai 980-8574, Japan. E-mail: akinoue@idac.tohoku.ac.jp

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Abstract

Objective: Epidermal growth factor receptor tyrosine kinase inhibitors are effective as first-line therapy for advanced non-small cell lung cancer patients harboring *epidermal growth factor receptor* mutations. However, it is unknown whether second-line platinum-based chemotherapy after epidermal growth factor receptor tyrosine kinase inhibitor therapy could lead to better outcomes. We evaluated the efficacy of second-line platinum-based chemotherapy after gefitinib for advanced non-small cell lung cancers harboring *epidermal growth factor receptor* mutations (the NEJ002 study).
Methods: Seventy-one non-small cell lung cancers, treated with gefitinib as first-line therapy and then receiving platinum-based chemotherapy as second-line therapy were evaluated in NEJ002. Patients were evaluated for antitumor response to second-line chemotherapy by computed tomography according to the criteria of the Response Evaluation Criteria in Solid Tumors group (version 1.0).
Results: Of the 71 patients receiving platinum-based chemotherapy after first-line gefitinib, a partial response was documented in 25.4% (18/71), stable disease in 43.7% (31/71) and progression of disease in 21.1% (15/71). The objective response and disease control rates were 25.4% (18/71) and 69% (49/71), respectively. There was no significant difference between first- and second-line chemotherapy in objective response and disease control rates for advanced non-small cell lung cancer

harboring activating *epidermal growth factor receptor* mutations. In the analysis of *epidermal growth factor receptor* mutation types, the objective responses of deletions in exon 19 and a point mutation in exon 21 (L858R) were 27.3% (9/33) and 28.1% (9/32), respectively, but these differences between objective response rates were not significant.

Conclusions: The efficacy of second-line platinum-based chemotherapy followed at progression by gefitinib was similar to first-line platinum-based chemotherapy, and *epidermal growth factor receptor* mutation types did not influence the efficacy of second-line platinum-based chemotherapy.

Key words: lung cancer, EGFR, mutation, gefitinib, second line

Introduction

Large randomized Phase III comparison trials have shown that epidermal growth factor receptor (EGFR) TKIs are effective as first-line therapy for advanced non-small cell lung cancer (NSCLC) patients harboring *EGFR* mutations (1–6). In one such Phase III comparison trial, the NEJ002 study, the first-line gefitinib group had a significantly higher objective response (73.7% vs. 30.7% in the chemotherapy group, $P < 0.001$), as well as a longer median progression-free survival (10.8 months, vs. 5.4 months, $P < 0.001$) (2,3). On the basis of these results, current guidelines recommend treatment of advanced NSCLC harboring *EGFR* mutations with EGFR TKI in the first-line setting (7,8). However, platinum-based chemotherapy had been considered the standard first-line treatment until the efficacy of first-line EGFR TKI was revealed for such patients (9,10). Therefore, it is not firmly established whether second-line platinum-based chemotherapy after EGFR TKI can lead to a good antitumor response. Thus, we evaluated the efficacy of such chemotherapy after lack of gefitinib response for advanced NSCLC harboring *EGFR* mutations in the NEJ002 study.

Patients and methods

Patients

The NEJ002 study was a multicenter, randomized, Phase III trial comparing gefitinib with carboplatin and paclitaxel (CBDCA/PTX) as first-line treatment for advanced NSCLC harboring sensitive EGFR mutations. Details of the study have been published previously. Of the 230 patients enrolled in the NEJ002 study, we retrospectively analyzed 114 patients treated with gefitinib as first-line therapy (Fig. 1). We selected 71 (62.3%) patients who received second-line platinum-based chemotherapy. Patients who did not receive second-line treatment or received EGFR TKI, or a non-platinum-based regimen, were excluded from the analysis. Eligibility criteria for NEJ002 included the presence of advanced NSCLC harboring activating *EGFR* mutations (excluding the resistant *EGFR* mutation T790M examined by the PNA-LNA polymerase chain reaction clamp method), no history of chemotherapy, age ≤75 years, performance status 0–1, appropriate organ functions and 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 with chemotherapy after first-line gefitinib

In the first-line setting, all patients in the gefitinib arm received 250 mg of gefitinib daily according to the NEJ002 protocol. After progression, patients received second-line chemotherapy with different regimens depending on the decision of the physician though the protocol recommended CBDCA/PTX as second-line chemotherapy. Detailed information on second-line chemotherapy after gefitinib treatment was assessed retrospectively for all patients.

Assessment procedures

After first-line gefitinib treatment, patient target lesions were assessed and second-line chemotherapy was then administered. Patients were evaluated for antitumor response to second-line chemotherapy with computed tomography scans of the head, chest and abdomen and a bone scan at an interval at the discretion of the physician. According to the NEJ002 protocol, treatment responses were defined as progressive disease, stable disease, partial response and complete response, in accordance with the criteria of the Response Evaluation Criteria in Solid Tumors group (RECIST, version 1.0). The efficacy of second-line platinum-based chemotherapy was evaluated for advanced NSCLC patients harboring *EGFR* mutations. In addition, the difference in efficacy and survival were analyzed for each *EGFR* mutation type.

Statistical analyses

Statistical analysis was performed using the statistical software package IBM SPSS Statistics 22 (IBM, Tokyo, Japan). Proportions were compared using the χ^2 test. Kaplan–Meier survival curves were drawn for overall survival and compared using a two-sided non-stratified log-rank test with a significance level of 0.05. The hazard ratio and its two-sided 95% confidence interval (CI) were calculated by Cox regression analysis including only the treatment arm as a covariate.

Results

Patient characteristics

Patient characteristics are shown in Table 1. The median age was 63 (range 43–75), and 63.4% of patients were female. The large majority of patients exhibited adenocarcinoma. Fifty-four patients had Stage IV (76.1%), and 47 patients were never smoker (66.2%). Thirty-seven (52.1%) patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, while for 34 (47.9%) PS was 1. There were no patients with ECOG PS ≥2. Thirty-three (46.5%) patients harbored in-frame deletions in exon 19, while 32 (45.1%) had tumors harboring amino acid replacement in exon 21, L858R. The objective response to first-line gefitinib was 78.9% [56/71: complete response (CR) = 2, partial response (PR) = 54], and disease control rate was 90.1% (64/71).

Regimens and efficacy of second-line platinum-based chemotherapy

Of the 82 patients treated with second-line therapy, 71 received platinum-based chemotherapy, 54 (76.1%) received CBDCA/PTX, 7 (9.9%) received carboplatin and pemetrexed (CBDCA/PEM),

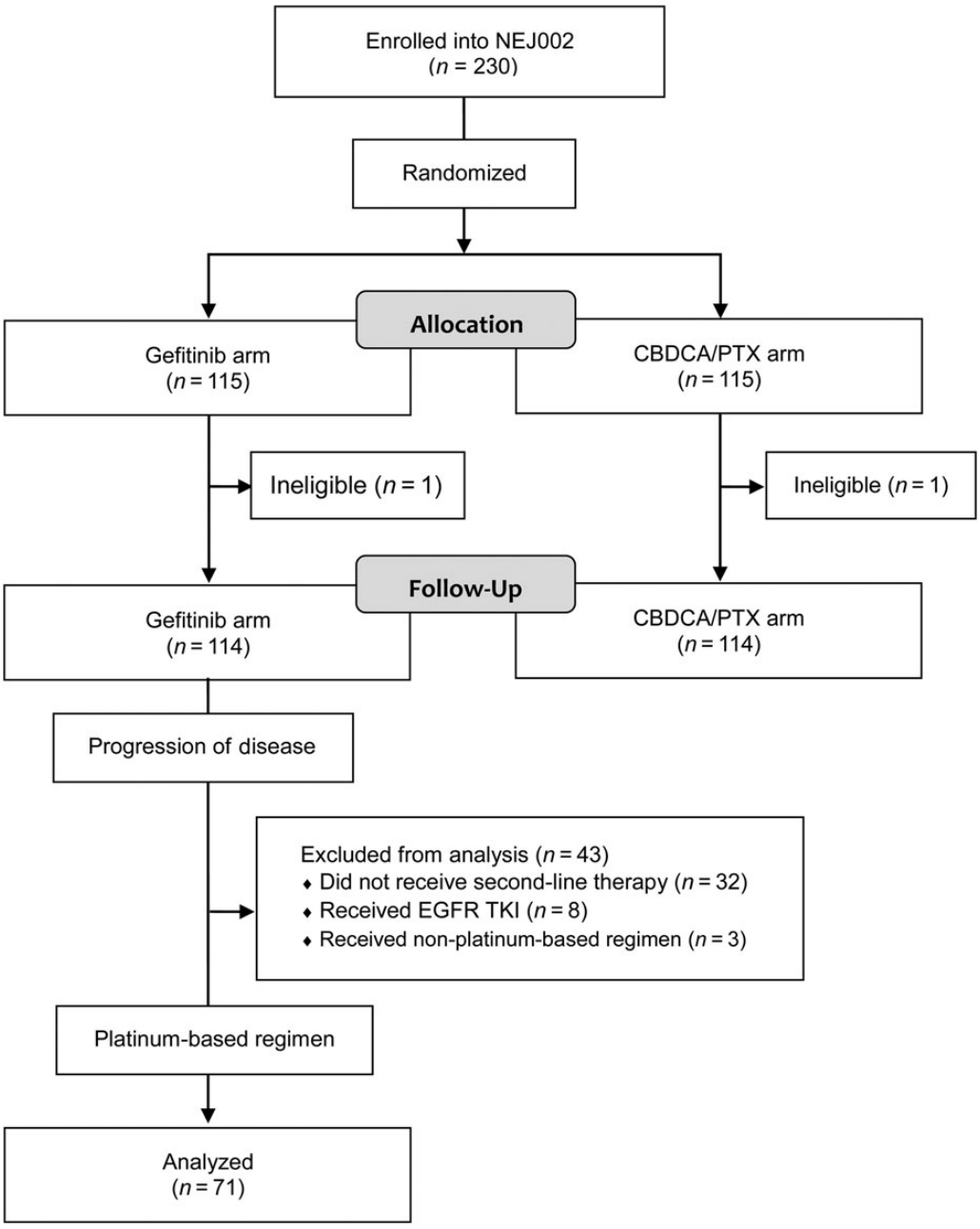


Figure 1. Flowchart of the patients analyzed in this study.

4 (5.6%) received cisplatin and pemetrexed (CDDP/PEM), 3 (4.2%) received carboplatin and gemcitabine (CBDCA/GEM), 2 (2.8%) received carboplatin and paclitaxel and bevacizumab (CBDCA/PTX/BEV) and 1 (1.4%) received cisplatin and vinorelbine (CDDP/VNR) (Table 2).

Of the 71 patients receiving platinum-based chemotherapy after first-line gefitinib, a partial response was documented in 25.4% (18/71), stable disease in 43.7% (31/71) and progression of disease in 21.1% (15/71). The objective response and disease control rates were 25.4% (18/71, 95% CI, 15.3–35.5%) and 69.0% (49/71, 95% CI, 58.2–79.8%), respectively. In the NEJ002 study, the objective response for first-line platinum-based chemotherapy was 30.7% (2). There was no significant difference in objective response between first- and second-line chemotherapy for advanced NSCLC harboring activating *EGFR* mutations (25.4%, vs. 30.7%, odds ratio 1.45, 95% CI 0.75–2.81, $P = 0.345$).

Overall survival with first- and second-line platinum-based chemotherapy

The median survival time of patients receiving platinum-based chemotherapy after first-line gefitinib was 28.9 months. In contrast, 112 (98%) patients received gefitinib after first-line CBDCA/PTX in the CBDCA/PTX arm of the NEJ002 study. The median survival time of these patients was 27.6 months. We compared MST of the patients receiving platinum-based chemotherapy included chemotherapy other than CBDCA/PTX after first-line gefitinib (Gefitinib → Platinum doublet chemo) with that of patients receiving gefitinib after first-line

CBDCA/PTX (CBDCA/PTX → Gefitinib) to evaluate the difference from the gefitinib treatment line (Fig. 2A). There was no significant difference in overall survival between first- and second-line chemotherapy (hazard ratio 0.77, 95% CI 0.52–1.14, $P = 0.188$). In addition, we compared MST of the patients receiving CBDCA/PTX after first-line gefitinib (gefitinib → CBDCA/PTX) with that of patients receiving gefitinib after first-line CBDCA/PTX (CBDCA/PTX → gefitinib), but these were not significantly different (Fig. 2B) (hazard ratio 1.03, 95% CI 0.69–1.52, $P = 0.888$).

Table 1. Patient characteristics

Characteristics	Value
No of patients	71
Age (range)	63 (43–75)
Sex	
Male	26
Female	45
Histologic type	
Adenocarcinoma	64
Large cell carcinoma	1
Adenosquamous cell carcinoma	1
Others	5
Clinical stage	
IIIB	9
IV	54
Post-operative recurrence	8
Smoking history	
Yes	24
No	47
ECOG performance status	
0	37
1	34
2	0
EGFR mutation type	
Exon19 del	33
Exon21 L858R	32
Others	6
First-line gefitinib response	
Complete response	2
Partial response	54
Stable disease	8
Progressive disease	6
Response that could not be evaluated[a]	1

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

[a]Because of exacerbation of mental illness.

EGFR mutation types and response to second-line platinum-based chemotherapy

EGFR mutation types and the responses to second-line platinum-based chemotherapy were analyzed. The objective responses to deletions in exon 19 (19 Del) and a point mutation in exon 21 (L858R) were 27.3% (9/33) and 28.1% (9/32), respectively, but these objective responses were not significantly different (odds ratio 0.96, 95% CI 0.32–2.84, $P = 0.841$). In addition, we analyzed median survival time for each major mutation. The median survival times were 32.7 months for 19 Del and 30.0 months for L858R, but these were not significantly different (hazard ratio 1.17, 95% CI 0.62–2.21, $P = 0.637$) (Fig. 3). In contrast, there was no case showing complete or partial responses in uncommon mutation types [0/6: stable disease (SD) = 2, progressive disease (PD) = 3, NE = 1]. However, there was no significant difference in objective response between common and uncommon *EGFR* mutation types ($P = 0.317$).

The association between response to prior gefitinib treatment and subsequent platinum-based chemotherapy

We investigated the association of response to second-line platinum-based chemotherapy with first-line gefitinib (Fig. 4). We categorized patients into two groups according to their treatment response with first-line gefitinib as follows: CR or PR cases for first-line gefitinib therapy and SD or PD cases. As a result, CR or PR cases showed a high objective response to second-line platinum-based chemotherapy compared with SD or PD cases, but the difference between the two groups was not significant (28% vs. 14%, odds ratio 2.4, 95% CI 0.482 to 11.95, $P = 0.452$).

Discussion

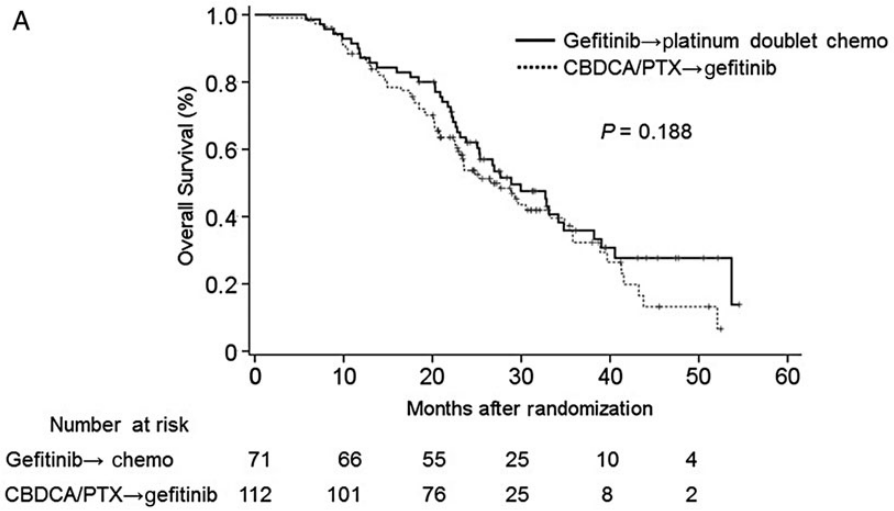
In this randomized Phase III study comparing gefitinib with CBDCA/PTX as first-line treatment for advanced NSCLC harboring *EGFR* mutations, we found that the efficacies of first and second-line platinum-based chemotherapy were similar. Among these, there was no significant difference in response and overall survival between 19 Del and L858R mutations. These results suggest that the efficacy of platinum-based chemotherapy was comparable among those with and without prior EGFR TKI therapy, indicating that second-line platinum-based chemotherapy is sufficiently efficacious in advanced NSCLC patients with *EGFR* mutations.

Many recently published studies showed favorable outcomes and tolerance to first-line EGFR TKI therapy in patients with the above

Table 2. Regimens and response of second-line platinum-based chemotherapy in NEJ002

Second-line platinum-based regimen	*n* (%)	CR	PR	SD	PD	Response that could not be evaluated	Response rate (%) (95% CI)	Disease control rate (%) (95% CI)
Total	71	0	18	31	15	7	25.4 (15.3–35.5)	69 (58.2–79.8)
CBDCA/PTX	54 (76.1)	0	16	23	12	3	29.6	72.2
CBDCA/PEM	7 (9.9)	0	1	2	2	2	14.3	42.9
CDDP/PEM	4 (5.6)	0	0	3	1	0	0	75.0
CBDCA/GEM	3 (4.2)	0	1	2	0	0	33.3	100
CBDCA/PTX/BEV	2 (2.8)	0	0	1	0	1	0	50.0
CDDP/VNR	1 (1.4)	0	0	0	0	1		

CBDCA/PTX, carboplatin and paclitaxel; CBDCA/PEM, carboplatin and pemetrexed; CDDP/PEM, cisplatin and pemetrexed; CBDCA/GEM, carboplatin and gemcitabine; CBDCA/PTX/BEV, carboplatin and paclitaxel and bevacizumab; CDDP/VNR, cisplatin and vinorelbine; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.



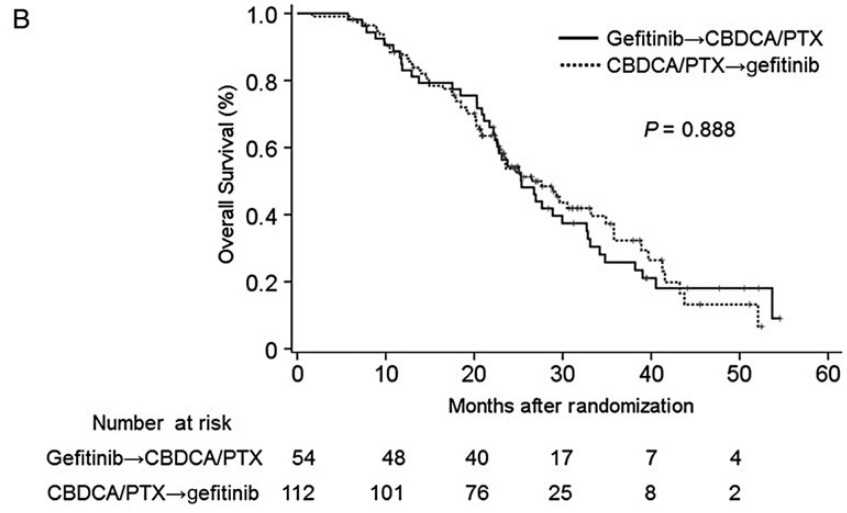


Figure 2. Kaplan-Meier curves for overall survival in the patients receiving (A) platinum-based chemotherapy and (B) CBDCA/PTX after first-line gefitinib with that of patients receiving gefitinib after first-line CBDCA/PTX.

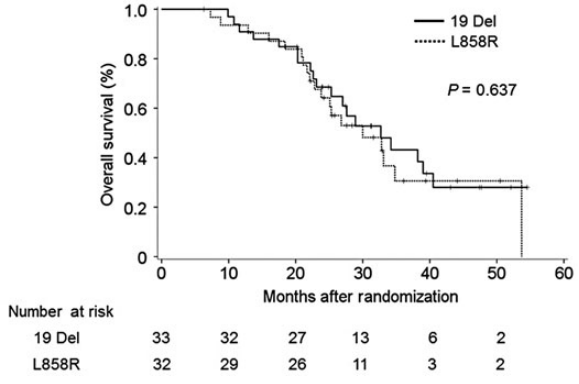


Figure 3. Kaplan-Meier curves for overall survival in the patients with 19 Del and L858R mutations.

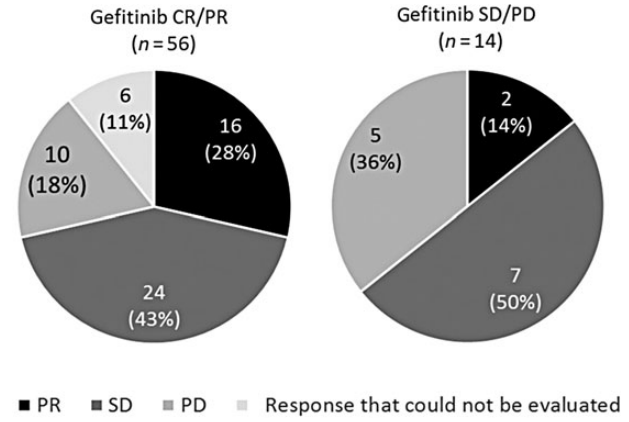


Figure 4. Association of response to second-line platinum-based chemotherapy with first-line gefitinib.

mutations (2–6,11–14). On the other hand, it is not known whether first-line platinum-based chemotherapy or such chemotherapy after failure of first-line therapy with EGFR TKI can result in similar treatment response outcomes. To our knowledge, the effect of second-line platinum-based chemotherapy for advanced NSCLC harboring *EGFR* mutations in a Phase III randomized trial has not been previously published. In Japanese randomized Phase III studies comparing gefitinib with platinum-based chemotherapy as first-line treatment for such cases, objective response and disease control rates were 30.7–32.2% and 78.0–79.8%, respectively (2–4). In the present retrospective analysis, the objective response and disease control rates on second-line platinum-based chemotherapy were 25.4% and 69.0%, respectively. Though we did not evaluate other regimens because of small numbers of cases, similar results were shown by analysis of carboplatin and paclitaxel cases only. These results were comparable with those reported in Phase III studies. In a similar previous study, Tseng et al. (15) retrospectively analyzed 61 advanced chemonaïve patients with *EGFR*-mutant lung adenocarcinoma and showed that prior EGFR TKI therapy did not influence the efficacy of subsequent therapy with pemetrexed plus platinum. These results indicated that first- and second-line platinum-based chemotherapy resulted in similar treatment responses in patients with *EGFR* mutations.

Previous randomized Phase III trials showed that EGFR TKIs are extremely effective for advanced NSCLC patients harboring EGFR mutations (1–6). In contrast, it is unknown whether differences in *EGFR* mutation type result in different efficacy of platinum-based chemotherapy. No retrospective study comparing responses of exon19, exon 21 and other uncommon *EGFR* mutations has been reported to date. In a recent study, Fang et al. reported relationships between *EGFR* mutation types and survival (16). Patients with the exon 19 *EGFR* mutation tended to have a longer median survival time and 1-year and 2-year overall survival than those with the exon 21 *EGFR* mutation (19.2 months, 90.6%, and 37.5% versus 17.8 months, 70.0%, and 30.0%, respectively), but the difference was not statistically significant. The objective response of these patients was not shown in the retrospective analysis. Our study suggested that objective response and disease control rate and overall survival were not different among *EGFR* mutation types which may therefore not influence the efficacy of platinum-based chemotherapy; furthermore, the difference with the gefitinib treatment line did not influence survival.

Our study also indicated that a good response to first-line EGFR TKI tended to favor a good response to second-line platinum-based chemotherapy. However, there was no significant difference between CR/PR and SD/PD cases treated with first-line EGFR TKI in NSCLC patients with *EGFR* mutations. In a study by Tseng et al. (15), there was no significant association between the efficacy of prior EGFR TKI and subsequent therapy with pemetrexed plus platinum. Although our results may have been influenced by the small sample size, they suggest that neither efficacy of first-line EGFR TKI therapy nor *EGFR* mutation type would influence the efficacy of subsequent platinum-based chemotherapy.

The present study has several limitations. First, it was a retrospective study with selected groups of patients. For this reason, almost all patients received CBDCA-based rather than CDDP-based regimens. Second, since this was a retrospective study, we did not include the evaluation of progression-free survival and confirmed response in the protocol in the second-line setting, as we were unable to obtain these data. In addition, responses to second-line chemotherapy were assessed by the individual investigator in each institution. Consequently, these factors might have influenced the evaluation of efficacy in the second-line treatment. Third, we failed to detect a significant difference of efficacy in the treatment line and *EGFR* mutation types, which may have been a result of the small sample size. Therefore, caution should be used when comparing our results with those of other studies.

In conclusion, we found that platinum-based chemotherapy appeared to be of benefit as a second-line treatment after gefitinib failure presented in patients with *EGFR* mutations. Our analysis indicated that the efficacy of second-line chemotherapy was similar to that of first-line chemotherapy, and *EGFR* mutation types did not influence the survival and efficacy of platinum-based chemotherapy. Future prospective studies with larger numbers of patients are warranted to definitively elucidate any differences in efficacy between treatment lines.

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Conflict of interest statement

Kunihiko Kobayashi, Akihiko Gemma, Yasuo Saijo and Toshihiro Nukiwa received research grants from AstraZeneca. Akira Inoue, Kunihiko Kobayashi, Makoto Maemondo, Hiroshi Isobe, Koichi Hagiwara and Toshihiro Nukiwa received lecture fees from AstraZeneca. All remaining authors have declared no conflicts of interest.

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