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Re-administration of osimertinib in osimertinib-acquired resistant non-small-cell lung cancer

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ABSTRACT

Background: Osimertinib is a tyrosine kinase inhibitor (TKI) that is an essential agent for the treatment of *epidermal growth factor receptor* (*EGFR*)-mutant non-small-cell lung cancer (NSCLC). However, there is no established strategy for treatment following acquired resistance to this agent. One potential strategy for treating acquired resistance to EGFR TKIs is re-administration, which has been evaluated mainly using first- or second-generation EGFR TKIs. However, no clinical data are available with which to determine the significance of re-administration of osimertinib, a third-generation EGFR TKI. The aim of this study was to evaluate the efficacy of re-administering osimertinib to patients who had acquired resistance to this agent.

Patients and methods: We reviewed the medical records of consecutive patients with advanced NSCLC harboring *EGFR*-activating mutations and secondary T790M, who had undergone osimertinib re-administration to treat acquired resistance.

Results: Seventeen patients were re-administered osimertinib after acquiring resistance to osimertinib. Of these, two received osimertinib to treat carcinomatous meningitis without any measurable lesion. Responses were evaluated in the remaining 15 patients. The objective response and disease control rates were 33% and 73%, respectively. Tumor shrinkage by osimertinib re-administration was associated with that due to initial osimertinib treatment (r = 0.585, 95% confidence interval [CI]: 0.104–0.844). In the remaining two patients without measurable lesions, one exhibited improved clinical symptoms following osimertinib re-administration. The median progression-free survival (PFS) time of all 17 patients was 4.1 months (95% CI: 1.9–6.7). The toxicity of re-administration was low, without interruption of the treatment due to adverse events (AEs). Most patients had grade 2 AEs or lower.

Conclusions: Re-administration of osimertinib for *EGFR*-mutant NSCLC yielded modest activity with tolerable toxicity.

1. Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are essential agents for the treatment of advanced non-small-cell lung cancer (NSCLC) harboring *EGFR*-activating mutations; a dramatic response to these agents has been observed [1–3]. However, acquired resistance inevitably develops within 1–2 years of treatment commencement, half of which is caused by the *EGFR* secondary mutation T790M [4,5]. Osimertinib is a third-generation EGFR TKI that was developed to overcome T790M-induced acquired resistance. This agent showed promising clinical results in the AURA3 study [4], with an objective response rate (ORR) of 62% and median progression-free survival (PFS) of 12.3 months in T790M-positive NSCLCs. A recent FLAURA study revealed that osimertinib is a potent first-line therapy in *EGFR*-mutant NSCLCs [6]. When used as a first-line therapy, osimertinib showed significantly longer PFS than that of first-generation

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EGFR TKIs (17.2 vs. 8.5 months; hazard ratio, 0.46, P < 0.001). However, even with this potent next-generation EGFR TKI, acquired resistance inevitably develops and there is no established strategy for treating NSCLCs under acquired resistance to osimertinib. Thus, cytotoxic chemotherapy is still the standard therapy for *EGFR*-mutant NSCLC after acquired resistance to osimertinib [5].

A potential strategy for treating acquired resistance to osimertinib is re-administration, the efficacy of which has mainly been evaluated in cases of acquired resistance to first- or second-generation EGFR TKIs [7–10]. However, there have been no reports of outcomes following re-administration of the third-generation EGFR TKI, osimertinib. Recently, we encountered a patient who responded to osimertinib re-administration [11]; this experience allowed us to systemically investigate the efficacy of this strategy. In this study, we retrospectively investigated the efficacy of osimertinib re-administration in patients with *EGFR*-mutant NSCLC who had developed acquired resistance to osimertinib.

2. Patients and Methods

2.1. Methods

We retrospectively analyzed the medical records of consecutive patients with advanced NSCLC harboring *EGFR*-activating mutations and secondary T790 M, who were treated with osimertinib at Okayama University Hospital from June 2016 to April 2018. Re-administration of osimertinib in this study was defined as administration after progression following initial osimertinib therapy and one or more subsequent chemotherapies. Re-administration after cessation of osimertinib due to adverse effects without disease progression was not included in the current analysis.

This study was conducted in compliance with the principles of the Declaration of Helsinki, and the institutional review board of our institution approved the protocol.

2.2. Assessment of efficacy and toxicity

The standard Response Evaluation Criteria for Solid Tumors (RECIST; ver. 1.1) was applied to evaluate the objective response rate based on computed tomography (CT). The disease control rate (DCR) was defined as the percentage of patients who had achieved a complete response, partial response or stable disease. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (v. 4.0).

2.3. Statistical considerations

The PFS time was defined as the time from starting osimertinib re-administration until the date of progressive disease (PD) or death from any cause. The overall survival (OS) time was defined as the time from starting osimertinib re-administration until the date of death from any cause. PFS and OS curves were constructed using the Kaplan–Meier product-limit estimator. All statistical analyses were conducted using STATA software (ver. 11.0; Stata Corp, College Station, TX, USA).

3. Results

3.1. Patients

A total of 57 patients were treated with osimertinib at Okayama University between June 2016 and April 2018. Of these patients, 22 had experienced no progression while on osimertinib at the time of analysis and the remaining 35 had disease progression while on osimertinib. Among the 35 acquired-resistance cases, osimertinib was not re-administered to 18 patients at the time of analysis (14 stopped treatment due to poor general condition before attempting the re-administration of osimertinib, 3 were receiving standard cytotoxic chemotherapy, and 1 was lost to follow-up) and the remaining 17 were treated with osimertinib re-administration after acquiring osimertinib resistance (radiographical disease progression, n = 15; clinical progression, n = 2) and subsequent interval therapies. A summary of the characteristics of the 17 patients is presented in Table 1. The median patient age was 68 years (range: 43–78 years), and there was a female predominance. All patients had adenocarcinoma histology; nine had ex19 del + T790 M and the remaining eight had ex21 L858R + T790 M. The median number of regimens prior to osimertinib re-administration was five. The median duration and number of regimens between initial osimertinib treatment and re-administration were 5.9 months and 1. The ORR and median PFS of initial osimertinib therapy were 47% (8/17) and 7.8 months, respectively. The majority of patients received standard chemotherapy regimens including platinum-doublet and decetaxel with/without ramcirumab before the re-administration of osimertinib (14/17), and fewer patients had immune checkpoint inhibitors (4/17).

Table 1
Patient characteristics.

Median age, years (range)	68 (43–78)
Gender (male/female)	6/11
ECOG PS 0/1/2/3	3/8/4/2
Smoking, median pack-years (range)	0 (0–45)
Histology (Ad/others)	17/0
EGFR mutation status	
(del + T790M / L858R + T790M)	9/8
Stage (IIB or IV/recurrence)	15/2
Efficacy of initial osimertinib treatment	
Response CR/PR/SD/PD	0/8/5/4
PFS, month (range)	7.8 (0.9–9.9)
Between initial osimertinib treatment and re-administration	
Interval period, months (range)	5.9 (0.6–19.0)
Interval regimen number (range)	1 (1–4)
Regimens of systemic therapy before re-administration	
Received platinum doublet and DOC with/without Ram	13/17
Received ICIs	4/17

ECOG PS, Eastern Cooperative Oncology Group performance status; Ad, adenocarcinoma; *EGFR*, epidermal growth factor receptor; del, exon 19 deletion mutation; L858R, exon 21 L858R point mutation; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival.
DOC, decetaxel; Ram, ramucirumab; ICI, immune checkpoint inhibitor.

3.2. Efficacy of osimertinib re-administration

Among the 17 patients who underwent osimertinib re-administration, efficacy was radiographically evaluated in 15. Partial response and stable disease were achieved in five and six patients, with an ORR of 33% and a DCR of 73%, respectively (Table 2). The remaining two patients had no radiographically evaluable lesions and osimertinib was re-administered for the treatment of carcinomatous meningitis. Of these two patients, one showed clearly improved symptoms, including

Table 2
. Response to osimertinib re-administration.

	N = 15
CR	0 (0%)
PR	5 (33%)
SD	6 (40%)
PD	4 (27%)
ORR	**33%**

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate.

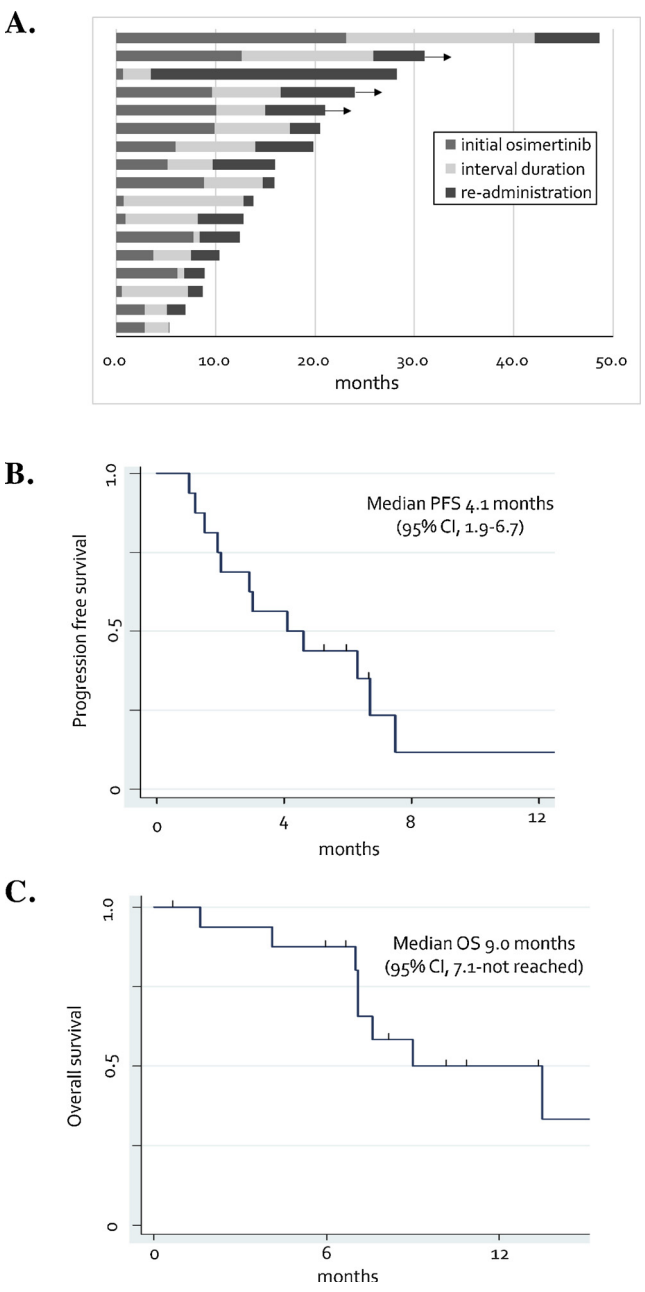

Fig. 1. A. Individual swimmer plots for each patient. Each bar depicts progression-free survival (PFS) on initial osimertinib treatment (gray), interval between initial osimertinib treatment and its re-administration (light gray), and re-administration (dark gray). Arrows indicate patients for whom osimertinib re-administration continued at the data collection cutoff time. **B. PFS with osimertinib re-administration. C. Overall survival with osimertinib re-administration.**

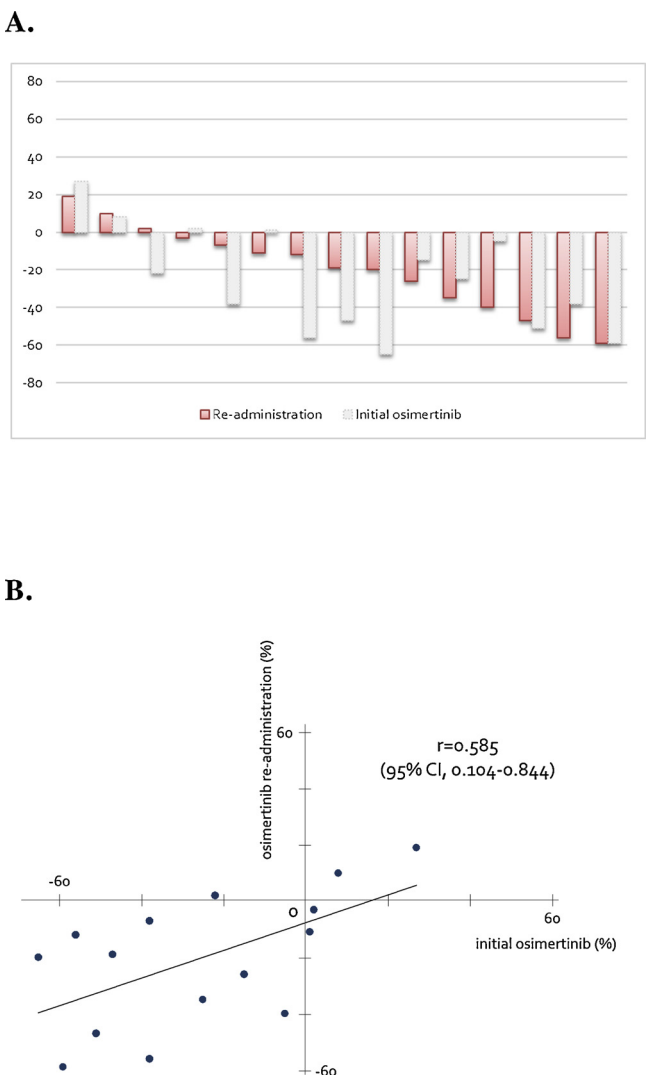

Fig. 2. A. Waterfall plot analysis with osimertinib, Waterfall plot of the percentage change in measurable tumors from baseline at the time of best response among 15 patients. Red bars represent responses to osimertinib re-administration. Adjacent gray bars represent responses to initial osimertinib treatment in the corresponding patient. **B. Correlation between initial osimertinib treatment and re-administration**, X-axis represents the percentage change in the tumor due to initial osimertinib treatment. Y-axis represents that due to osimertinib re-administration. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

headache and nausea. In total, 12 of the 17 patients (71%) received clinical benefit from osimertinib re-administration. Response durations are shown in Fig. 1A. The PFS was determined in all 17 patients (Fig. 1B). The median PFS was 4.1 months (95% confidence interval [CI]: 1.9–6.7) and the median OS was 9.0 months (95% CI: 7.1–not reached, Fig. 1C).

3.3. Correlation between efficacy of first osimertinib treatment and that of re-administration

A waterfall plot analysis of maximum tumor shrinkage from baseline is shown in Fig. 2A. This figure shows the responses to osimertinib re-administration (red) and initial osimertinib treatment (gray) for each patient. There seemed to be some positive relationship between the initial osimertinib treatment response and that to its re-administration. We further investigated the correlation using a scatter plot analysis (Fig. 2B). The response to initial osimertinib treatment was moderately correlated with that to re-administration (r = 0.585, 95% CI: 0.104–0.844).

Correlations with the PFS of initial osimertinib, length of interval period, and interval regimen number were also examined and none were found to be associated with the efficacy of osimertinib re-administration (data not shown).

3.4. Safety

The adverse events (AEs) experienced by patients are shown in Table 3. No patient stopped osimertinib treatment due to AE, or

Table 3
Adverse events.

Grade	No. of patients (%)			
	1	2	≥ 3	Any
Diarrhea	1 (6)	0 (0)	0 (0)	1 (6)
Stomatitis	2 (12)	0 (0)	0 (0)	2 (12)
Anorexia	1 (6)	0 (0)	0 (0)	1 (6)
Skin rash	2 (12)	0 (0)	0 (0)	2 (12)
Peripheral neuropathy	1 (6)	0 (0)	0 (0)	1 (6)
Neutropenia	2 (12)	0 (0)	0 (0)	2 (12)
Anemia	0 (0)	1 (6)	0 (0)	1 (6)
Platelets decrease	0 (0)	0 (0)	1 (6)	1 (6)
AST or ALT elevation	2 (12)	0 (0)	0 (0)	2 (12)
Creatinine elevation	0 (0)	1 (12)	0 (0)	1 (12)
Hypothyroidism	0 (0)	1 (6)	0 (0)	1 (6)
Thrombosis	0 (0)	0 (0)	1	1 (6)
Pneumonitis	0 (0)	0 (0)	0 (0)	0 (0)

Common Terminology Criteria for Adverse Events v4.0 were applied in the safety analysis. No treatment-related deaths were observed.
AST, aspartate aminotransferase; ALT, alanine aminotransferase.

experienced grade 4 AEs or worse. There was no drug-induced pneumonitis in the osimertinib re-administrated patients, while initial osimertinib treatment showed a pneumonitis rate of 7.0% (4/57). This was probably because osimertinib was re-administered only to those who did not develop pneumonitis in response to initial osimertinib. One patient had a grade 3 plate decrease and grade 3 venous thrombosis, both of which were considered to be caused by the cancer progression itself. No treatment-related deaths occurred due to osimertinib re-administration.

4. Discussion

Acquired resistance to osimertinib inevitably develops, and a number of resistance mechanisms can be classified into an EGFR-dependent mechanism, including acquired C797S mutation, and an EGFR-independent one, including bypass tracks and phenotypic transition [12–16]. Various efforts have been made, but unfortunately there is no current clinically available strategy to overcome osimertinib resistance.

One potential clinically available strategy to overcome resistance is re-administration, but there are no clinical data from which to determine the significance of the re-administration of osimertinib. In this study, we found moderate efficacy of osimertinib re-administration, with an ORR of 33% and a median PFS of 4.1 months. Furthermore, osimertinib re-administration was extremely safe, and there were no cases of interruption due to AEs. The re-administration of EGFR TKIs has been evaluated mainly using first-generation EGFR TKIs that were developed prior to osimertinib [7–10]. Gefitinib re-administration demonstrated a median PFS of 2.0–3.4 months [7–9]. We also investigated the efficacy of afatinib, a second-generation EGFR TKI, in *EGFR*-mutant NSCLC without T790 M after resistance to a first- or second-generation EGFR TKI. Re-administration of afatinib showed modest efficacy, with an ORR of 17% and a median PFS of 4.2 months [10]. Taken together, these results show moderate activity with re-administration of EGFR TKIs, with an ORR of 20–30% and a median PFS of 3–4 months. Given that the median OS of *EGFR*-mutant NSCLC is longer than 3 years, and that such patients require more treatment options, osimertinib re-administration could be a potent clinical treatment for *EGFR*-mutant NSCLC patients when the patients maintain good performance status even after progression to osimertinib and standard chemotherapies.

The extent of tumor shrinkage by osimertinib re-administration was moderately correlated with that of initial osimertinib treatment. Although the precise mechanisms underlying this phenomenon remain unclear, cancer cells with higher sensitivity to osimertinib, which are potentially more dependent on EGFR signaling, could retain their characteristics even after acquired resistance.

Osimertinib re-administration also showed excellent tolerability. The AEs of all patients except one were grade 2 or lower (Table 2). One patient had a grade 3 platelet decrease, which was deemed by the attending physician to be caused by the progression of the disease itself, not by osimertinib.

This study had some limitations. First, we retrospectively analyzed heterogeneous data with a small sample size, such that the results are somewhat speculative, rather than definitive. In fact, the ORR and median PFS of initial osimertinib treatment in our cohort were worse than those of the historical control [17]. Given that osimertinib has been clinically available for only 2 years in our country, and that many patients remain on initial osimertinib treatment, more patients with shorter response times may have been included in this analysis. Second, this study was conducted only in patients with T790M-positive NSCLC after acquired resistance to first- or second-generation EGFR TKIs. The recent FLAURA trial showed that osimertinib for treatment-naïve *EGFR*-mutant NSCLCs can extend PFS compared to first-generation EGFR TKIs [6]. Osimertinib is now among the most potent first-line treatments for treatment-naïve *EGFR*-mutant NSCLC. Further extensive investigations are needed to determine whether re-administration is also effective for NSCLCs that progressed after first-line osimertinib treatment. Third, actual resistance mechanisms to initial osimertinib therapy were not determined in the 17 re-challenged cases and, therefore, further investigation is needed to determine the type of resistance mechanisms for which osimertinib re-challenge would be effective. Thus, our results should be interpreted cautiously.

In conclusion, osimertinib re-administration had modest activity and low toxicity in the treatment of *EGFR*-mutant NSCLC that had acquired resistance to osimertinib.

Conflict of interest statement

EI received honoraria from AstraZeneca, Eli Lilly Japan, Boehringer Ingelheim, and Chugai Pharmaceutical. EI received additional research funding from Eli Lilly Japan and MSD. KH received honoraria from AstraZeneca, Eli Lilly Japan, Daiichi Sankyo Pharmaceutical, Boehringer Ingelheim, Nihon Kayaku, Taiho Pharmaceutical, Chugai Pharmaceutical, and Sanofi Aventis. KH received additional research funding from Eli Lilly Japan, MSD, and Chugai Pharmaceutical. All other authors declare no conflicts of interest regarding this study. TM received honoraria from Takeda Pharmaceutical, Kyowa Hakko Kirin, Chugai Pharmaceutical, Novartis Pharmaceutical, Otsuka Pharmaceutical, Astellas Pharmaceutical, AsahiKASEI, Sumitomo Dainippon Pharmaceutical, from Mochida Pharmaceutical, Bristol–Myers Squibb, Phizer, Nippon Shinyaku, Janssen Pharmaceutical, Celgene, Eisai, Mundipharma, and Meiji Seika Pharma. TM also received research funding from Akeda Pharmaceutical and Kyowa Hakko Kirin. KO received research grants from Boehringer Ingelheim and Novartis Pharmaceuticals, Japan. KK received honoraria from Eli Lilly Japan, Nihon Kayaku, AstraZeneca, Daiichi Sankyo Pharmaceuticals, Chugai Pharmaceuticals, Taiho Pharmaceuticals, Boehringer Ingelheim, and Sanofi Aventis.

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