Original Article

Osimertinib as first-line treatment for recurrent lung cancer patients with *EGFR* mutation

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Background: Although osimertinib was approved as adjuvant therapy for lung cancer patients with *EGFR* mutation in various countries, there is still some ongoing debate as osimertinib has been approved based on disease-free survival (DFS) rather than overall survival (OS). We curated a case series in which we documented patterns of recurrence and efficacy and safety of osimertinib after recurrence.

Methods: Patients who received osimertinib as first-line treatment for postoperative recurrence between September 2018 and January 2023 were included. Clinicopathological factors, duration of osimertinib treatment (DoT), and adverse events were collected and analyzed.

Results: Twenty patients received osimertinib [male, n=6; median age, 75 years (range, 55–85 years)]. The *EGFR* mutation type was L858R in 11 patients and exon 19 deletion in eight patients. The performance status (PS) was 0 or 1 in all but two patients, who had symptomatic brain metastasis and were therefore PS 3. The first site of postoperative recurrence was locoregional in five patients and distant in 15 patients, including seven with brain metastasis. As of February 2023, 10 patients were still on osimertinib, including three with brain metastasis. Patients with brain metastasis or poor PS had a considerably shorter DoT than their counterparts. Three patients with symptomatic brain metastasis or leptomeningeal metastasis initially responded to osimertinib, but all died of disease progression. Five patients discontinued osimertinib due to serious adverse effects (pneumonitis, drug eruption, and heart failure).

Conclusions: Although osimertinib exerts great disease control, even in patients with brain metastasis or poor PS, their presence was associated with a poor prognosis, even with osimertinib treatment. Therefore, adjuvant osimertinib is recommended unless contraindicated.

Keywords: Adjuvant therapy; osimertinib; molecular targeting therapy; relapsed resected non-small cell lung cancer (relapsed resected NSCLC); case series

Submitted Apr 01, 2023. Accepted for publication Aug 18, 2023. Published online Oct 10, 2023.
doi: 10.21037/jtd-23-537
View this article at: https://dx.doi.org/10.21037/jtd-23-537

Introduction

Osimertinib has been approved as adjuvant therapy in various countries following a positive result of superior disease-free survival (DFS) in the osimertinib arm with a hazard ratio of 0.17 among patients with stage II to IIIA disease (a primary endpoint). This phase III study (ADAURA), comparing osimertinib given daily for three years with placebo after complete resection of lung cancer with *EGFR* mutation, exceeded an expectation and the trial was unblinded in April 2020 (1). Furthermore,

the planned final analysis of overall survival (OS) has shown a better survival in osimertinib arm with a hazard ratio of 0.49, without reporting any new adverse events of special interest (2). Nevertheless, there is still an ongoing debate whether adjuvant osimertinib after surgical resection or starting osimertinib at disease recurrence is the best option.

In recent trials, including advanced non-small cell lung cancer, the study endpoints were mainly progression-free survival (PFS), or DFS for peri-operative adjuvant studies, because a meta-analysis showed that PFS could be a surrogate for OS (3). However, the meta-analysis was based on results obtained with cytotoxic drugs, not tyrosine kinase inhibitors (TKI). Although many phase III trials comparing EGFR-TKI with cytotoxic drugs failed to show an OS benefit (4-7), the FLAURA study, which compared osimertinib with 1st generation EGFR-TKI clearly showed better OS in the osimertinib arm (8). Similarly, adjuvant studies comparing 1st generation EGFR-TKI with cytotoxic chemotherapy, namely, CTONG1104 (9,10) and IMPACT (11), also failed to show benefits in terms of OS.

To answer this question, we curated a case series at our institution in which we documented patterns of recurrence and efficacy and safety of osimertinib after disease recurrence. We present this article in accordance with the STROBE and MDAR reporting checklists (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-537/rc).

Highlight box

Key findings

- Brain metastasis and a deteriorated performance status resulted in a poor outcome in recurrent *EGFR* mutated lung cancer patients who received 1st-line osimertinib treatment.

What is known and what is new?

- There is still some ongoing debate in the scientific community as osimertinib has been approved based on disease-free survival rather than overall survival.
- The treatment outcome is poor in patients with brain metastasis or with deteriorated performance status. Patients treated with osimertinib after disease recurrence have a high incidence of severe adverse events.

What is the implication, and what should change now?

- Adjuvant osimertinib is recommended unless contraindicated.

Methods

Patients

Consecutive patients who received osimertinib as first-line therapy after surgery at the Department of Thoracic and Breast Surgery, Oita University Faculty of Medicine between September 2018 and January 2023 were included. Those who underwent surgery without curative intent were excluded because we did not want to include patients with macroscopic disease (i.e., partial resection of the lung for diagnostic purposes in patients with advanced lung cancer). The pathological stage was defined based on the 8th edition of the American Joint Committee on Cancer lung cancer staging system and the histological classification (12) was determined based on the 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus and Heart (13). The efficacy and adverse events were collected from medical records on February 20th, 2023. Adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTC-AE) version 5.0 (14).

EGFR testing

EGFR mutation was determined by either CyCleave PCR (SRL Inc., Tokyo, Japan) or a cobas *EGFR* mutation detection kit version 2.0 (SRL Inc.), after extracting genomic DNA from formalin-fixed paraffin-embedded tissue sections from surgically resected primary tumors.

Statistical analysis

We chose the duration of osimertinib treatment (DoT) as an endpoint for efficacy, because disease recurrence in most patients was revealed by follow-up computed tomography (CT) or magnetic resonance imaging (MRI), they had no measurable disease. DoT was calculated as an actual period of osimertinib treatment, and those patients who were still on osimertinib and those patients who had ceased osimertinib because of adverse events were censored. The follow-up schedule in our institution was usually annual brain MRI and semi-annual chest CT in the postoperative setting (15), and more frequent after patients started osimertinib treatment for disease recurrence. The probability of survival was analyzed by the Kaplan-Meier

Table 1 Patient characteristics

Factors	Categories	Value
Age at recurrence, years		75 [55–85]
Sex	Male/female	6/14
PS at recurrence	0/1/2/3	15/3/0/2
Smoking	Never/ever	14/6
EGFR mutation	L858R/Del19/L861Q	11/8/1
Clinical stage	I/II/III	12/6/2
pStage[†,‡]	I/II/III/IVA	11/3/4/2
Post operative adjuvant	None/UFT/VP	13/5/2
First site of recurrence	Locoregional/distant	5/15
Brain metastasis (first site)	Positive[§]/negative	7/13
RFS, months		33.1 [0–141.1]

[†], for stage I, IA2/IA3/IB =3/3/5; [‡], two patients had pleural dissemination found intra-operatively, and therefore pStage IVA; [§], two patients had leptomeningeal metastasis. Data are presented as median [range] or number. PS, performance status; pStage, pathological stage; UFT, tegafur and uracil; VP, vinorelbine and cisplatin; RFS, recurrence-free survival.

method using the date of osimertinib introduction as the starting point. The log-rank test was used to determine the significance of differences between subgroups. The site of first recurrence was determined to be local if the patients experienced intrathoracic recurrence (pleural dissemination, malignant pleural effusion, pulmonary metastasis in the ipsilateral thoracic cavity or regional lymph nodes). If any distant metastasis was observed at recurrence along with local recurrence, the site of first recurrence was defined as distant. All statistical analyses were performed using EZR version 1.55 (16).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board at Oita University Faculty of Medicine (IRB No. 698), and informed consent was obtained from each patient.

Results

Patients' characteristics

During the period, 20 patients were identified to receive first-line osimertinib treatment after disease recurrence [male, n=6; median age, 75 years (range, 55–85 years)] (*Table 1*). The *EGFR* mutation type was L858R in 11 patients, exon 19 deletion (Del19) in 8 patients, and L861Q (uncommon mutation) in 1 patient. The performance status (PS) was 0 or 1 in all but two patients, who had central nervous system (CNS) metastasis and were therefore PS 3. The first site of postoperative recurrence was locoregional in 5 patients and distant in 15 patients, including 7 patients with CNS metastasis.

Duration of osimertinib treatment

As of February 2023, 10 patients were still on osimertinib, including 3 with CNS metastasis, and the median DoT was not reached (*Figure 1A*). Patients who had brain metastasis as the first site of recurrence experienced poorer outcomes (DoT not reached *vs.* 23.7 months, P=0.04, *Figure 1B*). PS was also related to DoT, although the number of patients with poor PS was small (DoT not reached in PS 0, 2.5 months in PS 1–3, P=0.0005, *Figure 1C*). Three patients with symptomatic brain metastasis (including two with leptomeningeal metastasis) initially responded to osimertinib, but died of disease progression after 23.7, 11.8, and 3.9 months of treatment, respectively. There were no significant differences in DoT according to age, sex, smoking, *EGFR* mutation type (*Figure 1D*), adjuvant therapy, clinical Stage, pathological Stage, first site of recurrence, or recurrence-free survival.

Adverse events, reasons for treatment discontinuation and mechanism of resistance

The treatment courses of individual patients are shown in *Figure 2*. Although five patients were unable to continue osimertinib due to serious adverse effects (pneumonitis, n=3; drug eruption, n=1; and heart failure, n=1), there was no treatment-related mortality. Among them, one patient switched to gefitinib after experiencing severe drug eruption (Stevens-Johnson syndrome, the 5th patient from the top, *Figure 2*). Another patient (the third patient from the top, *Figure 2*) switched to gefitinib because of financial issues, and ended up using osimertinib after disease progression during gefitinib treatment. The reason for osimertinib discontinuation was disease progression in other patients. The mechanism of resistance to osimertinib treatment was unknown, except for one patient (the third patient from the top, *Figure 2*), who had small cell transformation diagnosed

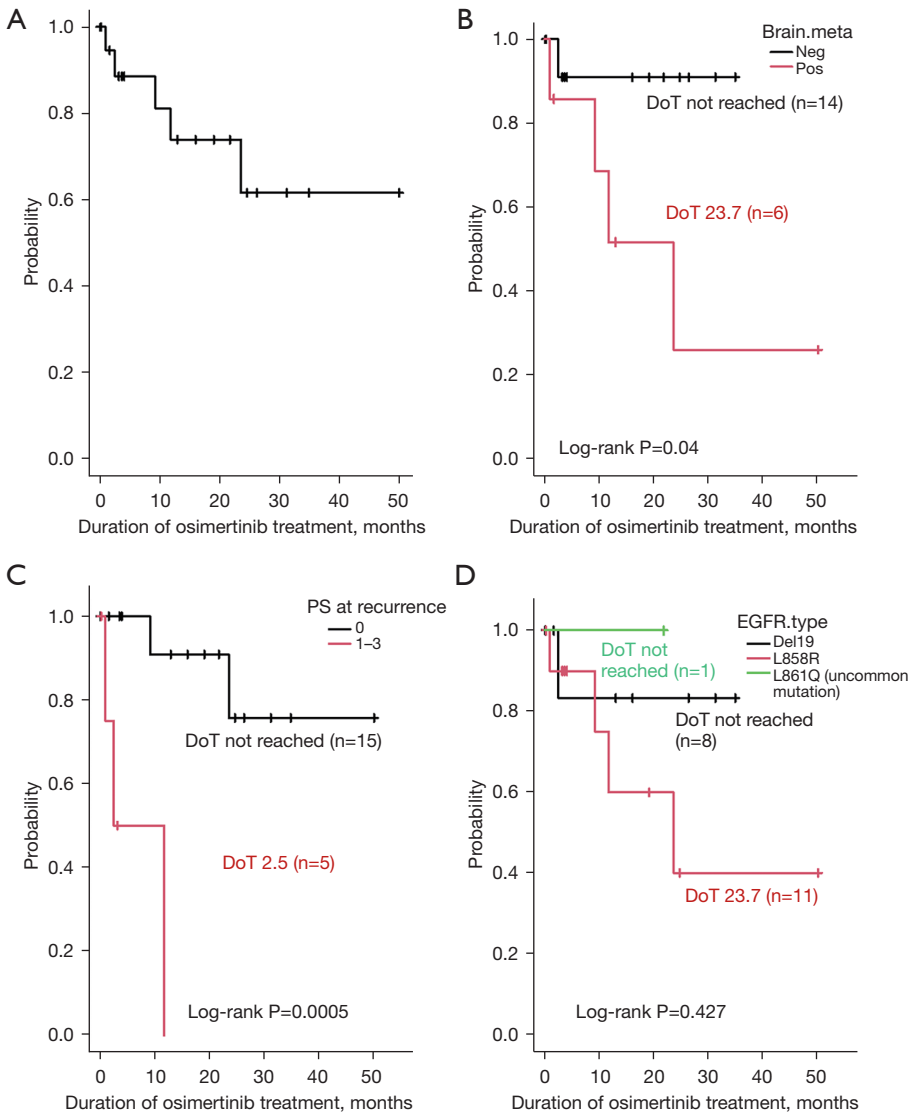

Figure 1 Duration of osimertinib treatment after recurrence in resected lung cancer patients with *EGFR* mutation. Kaplan-Meier curves for all 20 patients (A) according to the presence of brain metastasis (B); according to the performance status (C); and according to the *EGFR* mutation types (D). + indicates censored cases. PS, performance status; DoT, duration of osimertinib treatment.

from malignant pleural effusion and went on to receive carboplatin, etoposide and atezolizumab. At the time of writing this report, the patient remains on maintenance atezolizumab without evidence of disease progression.

Discussion

Osimertinib was developed for *EGFR* T790M, a major cause of acquired resistance to first- and second-generation EGFR-TKIs (17). Because osimertinib also demonstrates high specificity to activating *EGFR* mutations, it shows a very favorable toxicity profile (18). Therefore, it can also be delivered to patients with a deteriorated PS, elderly patients, and patients with co-morbidities. However, the PFS is shorter in patients with a poor PS, when they are treated with osimertinib (19-21).

CNS metastasis is a common event in lung cancer patients with *EGFR* mutation (22). Patients should be carefully examined for CNS metastasis with brain MRI, as it frequently leads to a decline in PS, analogous to the impact of bone metastasis. Although osimertinib is effective for patients with CNS metastasis, the PFS is shorter in those patients (23).

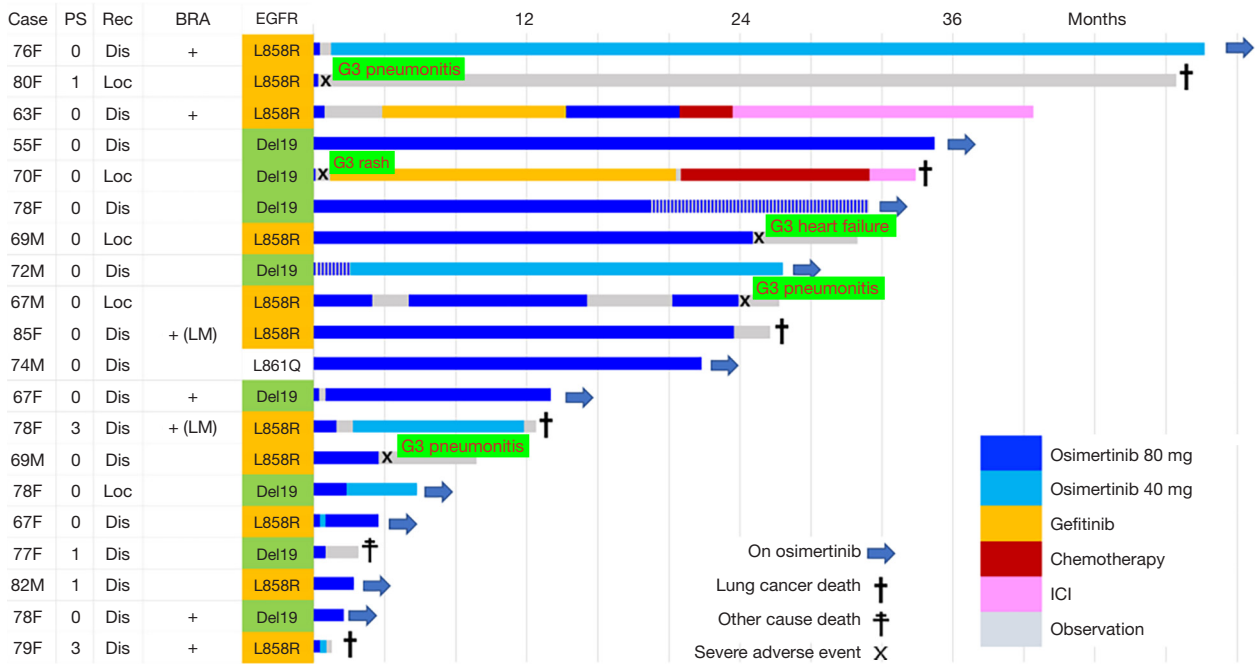

Figure 2 Treatment courses of individual patients listed according to the follow up time. F, female; M, male; PS, performance status; Rec, first site of recurrence; Dis, distant; Loc, locoregional; BRA, brain metastasis; LM, leptomeningeal metastasis; G3, grade 3 (Common Terminology Criteria for Adverse Event); ICI, immune checkpoint inhibitor.

It has been reported that the odds ratio of brain recurrence becomes the highest at 15 months after surgery (24). Furthermore, an analysis using proportional hazards competing risks and multistate models with data from the International Adjuvant Lung Cancer Trial revealed that platinum doublet could not reduce the risk of CNS metastasis (25). In the adjuvant setting, gefitinib or erlotinib could not effectively inhibit CNS recurrence (9,11), but osimertinib could (1). The difference between the drugs, especially in patients without CNS metastasis, is not clear. In patients with CNS metastasis, the CNS fluid penetration rates were similar between drugs with gefitinib being 1.13% to 1.30% (26,27) and osimertinib being 0.79% to 1.47% (28,29). It has been reported that the concentration of osimertinib in the CNS fluid is higher in comparison to other TKIs when they are delivered orally (30).

As for adverse events, the incidence of interstitial pneumonitis is the greatest concern in advanced lung cancer treated with osimertinib (all-grade, 3.9%; grade ≥3, 2.1%, FLAURA trial) (31), especially among the Japanese subset (all-grade, 12.3%; grade ≥3, 1.5%) (32). In this study, 3 patients developed grade 3 pneumonitis (15%); this incidence is higher in comparison to clinical trials, as is also reported in other real-world studies (33). However, no grade ≥3 pneumonitis was observed in the ADAURA study (1). This could be explained by the fact that the incidence of drug-related pneumonitis is related to smoking status and poor PS before treatment (34). In fact, in the ADAURA trial, 71.5% of the patients were never smokers and 64% had PS 0 (1), while in the FLAURA trial, 64% were never smokers and 41% had PS 0 (31). Even when the discontinuation of osimertinib is required due to grade 1–2 pneumonitis (33,35), the careful re-administration of osimertinib when the patient experiences recurrence is feasible (36,37). There are also studies showing that the re-administration of TKIs after disease recurrence is safe and effective (38,39).

Although most patients receive benefit from adjuvant osimertinib, there may still be a group who does not require adjuvant treatment. Circulating tumor DNA might be helpful in patient selection and treatment monitoring (40). We had eight patients who experienced recurrence even though their pathological stages were IA–IB. Several studies reported the risk factors for recurrence in patients with completely resected stage I lung cancer (41), and the ADAURA2 study is ongoing for high-risk stage I patients (42). Concomitant molecular alteration is also important in predicting the response to adjuvant EGFR-TKI. *NKX2-1*

gain, *CDK4* gain, *TP53* mutation, and *MYC* gain have been reported to predict significantly better survival in patients who receive adjuvant EGFR-TKI (43). We reported that *NOTCH1* and *CTNNB1* mutations exist as an early event, and remain after acquired resistance (44). For these events, there might be a strategy to enhance EGFR-TKI treatment by combining treatment, such as NOTCH inhibitors (45,46) or Cyclin-dependent kinase 4/6 inhibitors (47).

Conclusions

In conclusion, our data showed a favorable overall response to osimertinib in patients with postoperative recurrence, but patients with brain metastasis or with poor PS showed a poor prognosis. While starting osimertinib at recurrence effectively rescues most patients, recurrence with poor PS and brain metastasis is associated with abysmal outcomes; since the drug is well tolerated, starting treatment in the adjuvant setting is sensible.

Acknowledgments

The authors would like to thank Dr. Brian Quinn, Editor-in-Chief, Japan Medical Communication, Fukuoka, Japan for his critical comments on the manuscript.
Funding: This work was supported by KAKENHI, Japan Society for the Promotion of Science, Tokyo, Japan [Nos. JP 21K08889 (AO) and 20K09168 (KS)].

Footnote

Reporting Checklist: The authors have completed the STROBE and MDAR reporting checklists. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-537/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-537/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-537/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-537/coif). AO has received speakers bureaus from AstraZeneca (Cambridge, UK), Chugai Pharmaceutical (Tokyo, Japan), MSD Japan (Tokyo, Japan), Bristol Myers Squibb (Tokyo, Japan), and Ono Pharmaceutical (Tokyo, Japan), and on the Advisory Board for AstraZeneca (Cambridge, UK). AO reports grant from the Japan Society for the Promotion of Science (No. JP 21K08889). KS has received grants from AstraZeneca (Cambridge, UK), Chugai Pharmaceutical (Tokyo, Japan), MSD Japan (Tokyo, Japan), Bristol Myers Squibb (Tokyo, Japan), and Ono Pharmaceutical (Tokyo, Japan), speaker and consultant honoraria from AstraZeneca (Cambridge, UK), Chugai Pharmaceutical (Tokyo, Japan), MSD Japan (Tokyo, Japan), Bristol Myers Squibb (Tokyo, Japan), and Ono Pharmaceutical (Tokyo, Japan), and on the Advisory Board for AstraZeneca (Cambridge, UK) and Chugai Pharmaceutical (Tokyo, Japan). KS reports grant from Japan Society for the Promotion of Science (No. JP 20K09168). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board at Oita University Faculty of Medicine (IRB No. 698), and informed consent was obtained from each patient.

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Cite this article as: Osoegawa A, Karashima T, Takumi Y, Sato T, Abe M, Hashimoto T, Sugio K. Osimertinib as first-line treatment for recurrent lung cancer patients with *EGFR* mutation. J Thorac Dis 2023;15(10):5566-5573. doi: 10.21037/jtd-23-537

