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Epidermal growth factor receptor-Mutated Non-small-cell Lung Cancer with Intracranial Progressions and Stable Extracranial Diseases Benefit from Osimertinib Regardless of T790M Mutational Status

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Abstract

Objectives: Osimertinib has exhibited promising central nervous system (CNS) efficacy in Epidermal growth factor receptor (EGFR)-mutated advanced non-small-cell lung cancer (NSCLC) patients. In real-world clinical practice, patients would turn to plasma genotyping or take osimertinib blindly after CNS progression on previous tyrosine kinase inhibitors (TKIs). However, the efficacy of osimertinib in those patients according to their T790M mutational status has not been explored.

Materials and methods: Twenty-five patients who received osimertinib due to intracranial progressions with stable extracranial diseases after early-generation EGFR-TKI treatment were collected from 1032 EGFR-mutated NSCLC. Plasma samples were analyzed for EGFR mutations using next-generation sequencing (NGS) or polymerase chain reaction (PCR).

Results: Among the 25 patients, 17 patients took plasma genotyping before osimertinib treatment with 8 patients EGFR T790M mutation-positive and the rest started osimertinib blindly. The median progression-free survival (PFS) was 8.0 months (95% confidence interval [CI]: 6.12-9.94) and median intracranial PFS (iPFS) was 14.4 months (95% CI: 7.27-21.59) for the total population. No statistical difference was found in PFS and iPFS among patients with different EGFR T790M mutational statuses. Intracranial disease control rate (DCR) was 100.0% for 14 patients with evaluable intracranial lesions despite different T790M mutational statuses. DCR for extracranial lesions and overall lesions were 100.0%, 66.7%, and 87.5% for patients with T790M, no T790M, and unknown T790M mutational status, respectively.

Conclusion: For EGFR-mutated NSCLC patients with only intracranial progressions after previous TKI treatments, osimertinib is a promising treatment option regardless of T790M mutational status from plasma genotyping.

Keywords

non-small-cell lung cancer, intracranial metastases, genotyping, osimertinib, precision medicine

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Introduction

Epidermal growth factor receptor (EGFR)-mutated non-small-cell lung cancer (NSCLC) patients have a much higher risk of developing central nervous system (CNS) metastases.[1] As the survival of EGFR-mutated NSCLC is prolonged by EGFR tyrosine kinase inhibitor (TKI), patients have an increased incidence to develop the CNS metastases because CNS is a sanctuary site for tumor cells owing to the presence of the blood-brain barrier. For CNS metastases, the median overall survival (OS) is approximately 12 months for EGFR-mutated NSCLC patients with brain metastases (BM) and is about 9 months for EGFR-mutated NSCLC patients with leptomeningeal metastases (LM).[2,3] Existing therapies, such as whole-brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS), can bring neurologic side effects and delay the start of systemic therapy.[4,5]

Osimertinib is a third-generation, irreversible EGFR-TKI which has been approved for patients with EGFR-mutated advanced NSCLC and patients with T790M-positive NSCLC after disease progression on first/second-generation EGFR TKIs. Osimertinib has demonstrated better CNS penetration than gefitinib, rociletinib (CO-1686), or afatinib, as evidenced by a preclinical study of brain distribution.[6] The clinical trial has demonstrated that osimertinib has superior CNS efficacy than platinum-pemetrexed in T790M-positive advanced NSCLC.[7] Pooled analyses of two phase-II studies, AURA extension, and AURA2 demonstrated promising efficacy of osimertinib in measurable CNS lesions with EGFR T790M, of which the CNS ORR and disease control rate (DCR) were 54% and 92%, respectively.[8] The BLOOM study showed meaningful therapeutic efficacy of osimertinib in EGFR-mutated NSCLC patients with LM and revealed a median overall survival (OS) of 11.0 months.[9]

EGFR-mutated NSCLC patients with oligo-progression after previous TKI treatment may have their new lesions treated but continue on their TKI, according to the guidelines.[10] However, when patients have no obvious CNS symptoms, adding local treatment such as operation and radiotherapy will instead seriously affect patients' quality of life. Therefore, most patients tend to re-biopsy to identify the potential intracranial resistance mechanisms and take next-generation TKI. Since tumor tissue genotyping is technically difficult for CNS lesions and cerebrospinal fluid (CSF) is unsuitable for many patients' physical condition, in real-world clinical practice, most patients who have intracranial oligo-progressions turn to plasma genotyping or take the osimertinib blindly. Nevertheless, there is no clinical evidence supporting this medical practice. In this real-world study, we try to explore the efficacy of osimertinib according to the T790M mutational status from plasma genotyping in this special clinical situation.

Methods

Study Population

One thousand and thirty-two EGFR-mutated NSCLC patients who received osimertinib treatment were retrospectively collected between Jan 1, 2018, and Dec 30, 2020, in Sun Yat-sen University Cancer Center. Thirty-one patients who started osimertinib due to intracranial progressions with stable extracranial diseases after previous TKI were further identified. Six patients were lost to follow-up and 25 patients were finally enrolled for analysis in this study (Figure1).

All patients had been histologically confirmed NSCLC and activating EGFR mutations. Positive intracranial progressions and stable extracranial diseases after previous TKI treatment were confirmed by brain magnetic resonance imaging (MRI) and extracranial computed tomography (CT), respectively. Plasma samples were collected and analyzed for EGFR mutations using next-generation sequencing (NGS) or polymerase chain reaction (PCR). Patient data were collected through digital medical records. We have de-identified all patient detail. All included patients from our institute provided signed informed consent. The study was approved by Sun Yat-sen University Cancer Center Institutional Review Board.

Follow-up

To analyze clinical outcomes, progression-free survival (PFS) was measured and defined as the time interval from the start of the osimertinib treatment until progressive disease (PD) or death from any other causes, whichever occurs first; intracranial PFS (iPFS) was defined as the time from osimertinib treatment until intracranial progression. Disease response to treatment and tumor shrinkage was assessed according to Response Evaluation Criteria in Solid Tumor (RECIST) criteria (version 1.1). DCR was defined as the occurrence of complete response (CR), partial response (PR), or stable disease (SD).

Statistical Analysis

Survival analysis was performed using the Kaplan-Meier method with log-rank *P* values and 95% confidence

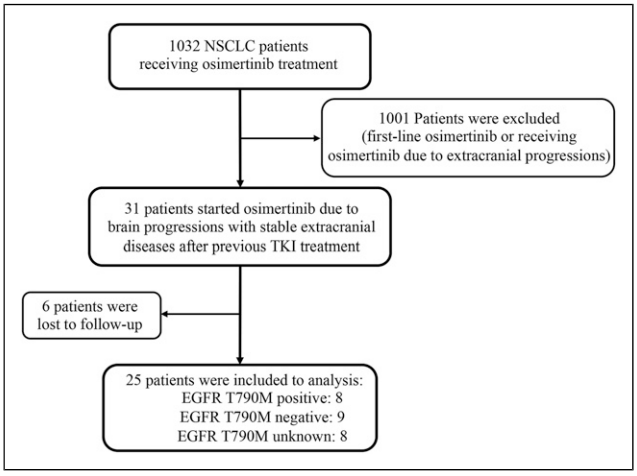

Figure 1. Patient flow of the study design.

interval (CI) reported. All statistical tests were two-sided; *P* value <.05 was deemed statistically significant. Univariate analysis was performed using interactive Cox proportional hazard regression. SPSS version 26.0 (SPSS, Chicago, IL) was used for statistical analyses and R software (version R 3.5.1) for making graphs.

Results

Patient Characteristics

Among the 25 patients, 17 patients received gefitinib (68.0%), 5 patients received erlotinib (20.0%); 2 patients received both (4.0%), and only 1 patient received icotinib (8.0%) before taking osimertinib. After developing intracranial progressions, 17 patients chose to take plasma genotyping before osimertinib treatment with 8 patients EGFR T790M mutation-positive and 9 patients EGFR T790M mutation-negative; the other 8 patients started on osimertinib directly with unknown T790M mutational status (supplementary methods). The median age of patients for this analysis was 54 (range: 37-75) years. Approximately two-thirds of the patients were female (64.0%) and never-smokers (76.0%). Except for one patient who was adenosquamous lung cancer, all patients were adenocarcinoma. Primarily, 10 patients (40.0%) and 14 patients (56.0%) harbored the EGFR exon 19 deletion and exon 21 L858 R substitution, respectively, only 1 patient (4.0%) had both mutations. Patients receiving osimertinib as the second-, third-, or > third-line treatment were 16 (64.0%), 7 (28.0%), and 2 (8.0%), respectively. Only 7 patients (28.0%) received brain radiotherapy before or at the same time with osimertinib treatment. Baseline characteristics of the study population are shown in Table 1. The associations between clinical factors and PFS were presented in Supplemental Table 1.

Clinical Outcomes

At data cutoff (Jun 5, 2021), 3 (12.0%) patients were still receiving osimertinib, and the median PFS for the total population was 8.0 months (95% CI:6.12-9.94) (Figure 2A). Intracranial progressions were observed in 15 patients (60.0%), and the median iPFS was 14.4 months (95% CI:7.27-21.59) (Figure 2C). The median PFS was 7.5 months (95% CI: 4.80-10.15), 8.0 months (95% CI: 2.98-13.09), and 7.3 months (95% CI: 4.67-9.93) for patients with T790M, no T790M, and unknown T790M mutational status, respectively. The median iPFS was 14.4 months (95% CI: 2.58-26.29), 12.4 months (95% CI: 3.84-20.97), and 14.7 months (95% CI: 6.45-22.95) for patients with T790M, no T790M, and unknown T790M mutational status, respectively. We found no difference in both PFS (P=.922) and iPFS (P=.767) according to T790M mutational status (Figure 2B and D). For the 18 patients who received osimertinib without radiotherapy, the median PFS and median iPFS were 8.0 months (95% CI: 5.95-10.11) (Supplemental Figure 3A) and 12.4 months (95% CI: 5.90-18.90), respectively (Supplemental Figure 3C). The median PFS was 7.5 months (95% CI: 6.00-8.93), 12.4 months (95% CI: 3.44-21.36), and 7.3 months (95% CI: 4.95-9.65) for patients with T790M, no T790M, and unknown T790M mutational status, respectively. The median iPFS was 8.8 months (95% CI: 1.76-15.91), 17.9 months (95% CI: 9.72-26.14), and 7.3 months (95% CI: 4.95-9.65) for patients with T790M, no T790M, and unknown T790M mutational status, respectively. No statistical difference in both PFS (P=.593) and iPFS (P=.482) for the population without radiotherapy according to T790M mutational status was found (Supplemental Figure 3B and D). Taking the basic EGFR mutational status into consideration, after excluding the patient with both 19del mutation and L858R mutation, we found that patients harboring EGFR 19del had a longer PFS and iPFS than patients harboring EGRF L858R mutation (median PFS: 12.4 months [95% CI:2.24-22.57] vs. 6.8 months [95% CI: 5.46-8.14], P=.042; median iPFS: 17.9 months [95% CI: 10.49-25.37] vs. 8.0 months [95% CI: 5.63-10.43], P=.011) (Supplemental Figures 1A and 2A). No statistical difference in PFS and iPFS was found between patients who had received radiotherapy and those who had not (median PFS: 6.6 months [95% CI: 5.88-7.26] vs. 8.0 months [95% CI: 5.95-10.11], P=.723; median iPFS: 22.1 months [95% CI: 9.00-35.26] vs. 12.4 months [95% CI: 5.90-18.90], P=.760) (Supplemental Figure 1B and 2B).

As regards the response rate, 14/25 patients had evaluable intracranial lesions and 11/25 had intracranial lesions <1 cm which were unevaluable. Of the 14 patients with evaluable intracranial lesions, intracranial DCR were all 100.0% for patients with T790M, no T790M, and unknown T790M mutational status, with 2 patients with no T790M and 2 patients with unknown T790M reached PR. Among the 11 patients with unevaluable intracranial lesions, 9/11 (81.8%) of them experienced a reduction of their brain lesions and the rest had a stable brain lesion. No statistical difference in PFS and iPFS was found between patients with evaluable intracranial lesions and those with unevaluable intracranial lesions (median PFS: 8.0 months [95% CI: 5.15-10.91] vs. 7.5 months [95% CI: 5.28-9.66], P=.557; median iPFS: 14.7 months [95% CI: 5.51-23.89] vs. 8.8 months [95% CI: 1.02-16.64], P=.530) (Supplemental Figure 4A and 4B). DCR for extracranial lesions and overall lesions were 100.0%, 66.7%, and 87.5% for patients with T790M, no T790M, and unknown T790M mutational status, respectively (P=.165) (Table 2). All patients reported no obvious adverse reactions during the treatment of osimertinib.

Genetic Examination After Progression on Osimertinib

Events of progression (regardless of intracranially or extracranially) were observed in 22/25 (88.0%) patients with 13 patients experiencing intracranial progressions, 7 patients experiencing extracranial progressions, and 2 patients experiencing both intracranial and extracranial progressions

Table 1. Patient Demographic and Baseline Characteristics.

Characteristics	EGFR T790M Positive No (%)	EGFR T790M Negative No (%)	EGFR T790M Blind No (%)	Total No (%)
No. Of patients	8	9	8	25
Median age, years (range)	47.5 (34-56)	55 (42-75)	56.5 (38-69)	54 (34-75)
Sex				
Female	7 (87.5)	6 (66.7)	3 (37.5)	16 (64.0)
Male	1 (12.5)	3 (33.3)	5 (62.5)	9 (36.0)
Histology				
Adenocarcinoma	7 (87.5)	9 (100)	8 (100)	24 (96.0)
Adenosquamous carcinoma	1 (12.5)	0	0	1 (4.0)
Smoking status				
Never	8 (100)	7 (77.8)	4 (50.0)	19 (76.0)
Former	0	2 (22.2)	4 (50.0)	6 (24.0)
Initial EGFR mutation				
EGFR 19del	3 (37.5)	4 (44.4)	3 (37.5)	10 (40.0)
EGFR L858R	5 (62.5)	5 (55.6)	4 (50.0)	14 (56.0)
EGFR 19del+L858R	0	0	1 (12.5)	1 (4.0)
Osimertinib line				
2nd	4 (50.0)	7 (77.7)	5 (62.5)	16 (64.0)
3rd	3 (37.5)	2 (22.2)	2 (25.0)	7 (28.0)
>3rd	1 (12.5)	0	1 (12.5)	2 (8.0)
EGFR-TKIs prior to osimertinib				
Gefitinib	8 (100)	5 (55.6)	4 (50.0)	17 (68.0)
Erlotinib	0	3 (33.3)	2 (25.0)	5 (20.0)
Icotinib	0	0	1 (12.5)	1 (4.0)
Gefitinib; Erlotinib	0	1 (11.1)	1 (12.5)	2 (8.0)
Previous radiation therapy				
No	7 (87.5)	7 (77.8)	4 (50.0)	18 (72.0)
Yes	1 (12.5)	2 (22.2)	4 (50.0)	7 (28.0)

(Supplemental Table 2). Of the 22 patients who progressed upon osimertinib, 9 patients were further analyzed for potential resistance mechanisms by NGS (Supplemental Table 3). All of the 9 patients were found to be T790M negative regardless of their T790M mutational status before osimertinib treatment. EGFR-related resistance mechanisms were identified: one patient was found harboring EGFR G724S; one patient was found harboring PTEN E299*; and two patients were found harboring EGFR amplification. Possible EGFR-independent resistant mechanisms were also spotted in other patients, including FGF amplification, KRAS amplification, and MYC amplification.

Cases With Different T790M Mutational Statuses Reached Intracranial PR

Three patients with different T790M mutational statuses before osimertinib treatment were retrospectively included to evaluate the antitumor activity and safety of osimertinib. Representative MRI brain scans from the three patients are taken at baseline and after the administration of osimertinib (Figure 3).

T790M positive: a 62-year-old Chinese female never-smoker was diagnosed with advanced EGFR L858R-positive NSCLC in April 2014. Gefitinib was chosen as first-line therapy (from April 2014 to April 2017). A combination of intravenous carboplatin, pemetrexed, and bevacizumab was administered as second-line treatment (May 2017 to July 2018). Therapy was interrupted as the patient rapidly progressed in August 2018, with metastatic lesions in the CNS. Following plasma genotyping revealed an EGFR T790M mutation. The patient started osimertinib (80 mg QD) in September 2018. The brain lesions diminished significantly following the treatment with osimertinib (Figure 3A).

T790M negative: a non-smoking, 62-year-old Chinese woman was diagnosed with advanced EGFR 19del-positive NSCLC in August 2018. The patient progressed after first-line gefitinib therapy (from August 2018 to November 2019), with a brain MRI showing enlarged brain lesions. The patient started to take osimertinib (80 mg QD) in November 2019 despite the negative T790M mutation of plasma genotyping. Subsequent brain MRI revealed an obvious shrinkage of initial brain lesions (Figure 3B).

Unknown T790M: a 56-year-old Chinese male smoker was diagnosed with advanced EGFR L858R-positive NSCLC in November 2018. The patient started taking gefitinib in December 2018 until MRI revealed brain progression in

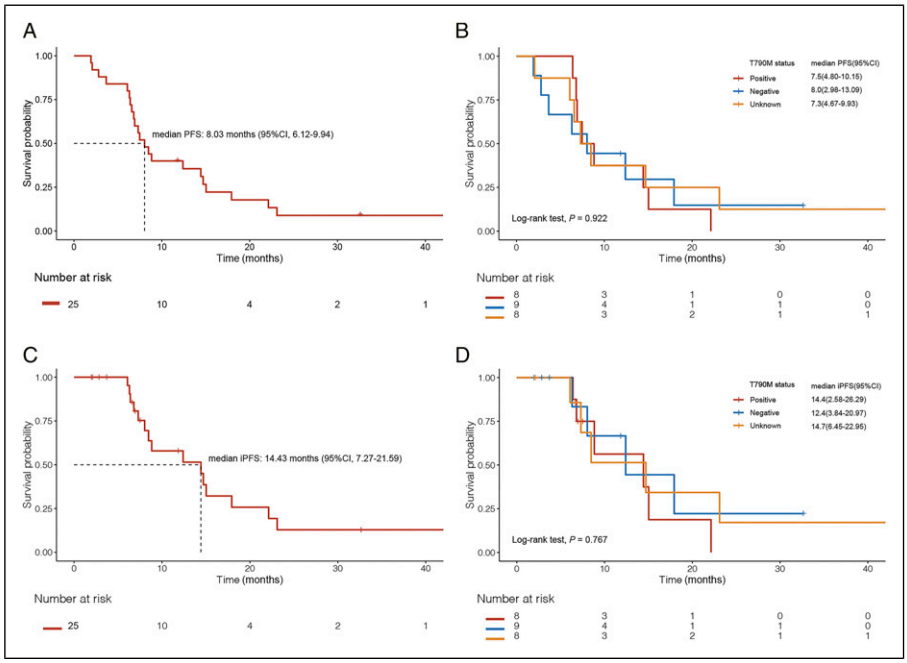

Figure 2. Kaplan-Meier curves of PFS for (A) total populations and (B) according to T790M mutational status; iPFS for (C) total populations and (D) according to T790M mutational status. CI, confidence interval; PFS, progression-free survival.

November 2019. The patients chose to take osimertinib directly (80 mg QD) in December 2019, without taking any genetic testing. Brain MRI after 3 months revealed an obvious shrinkage of primary brain lesions (Figure 3C).

Discussion

In our study, we report that EGFR-mutated NSCLC patients with only intracranial progressions after previous TKI treatments can benefit from osimertinib treatment regardless of T790M mutational status from plasma genotyping. With predictive biomarkers emerging in lung cancer patients, biopsy at progression becomes a necessity for guiding the subsequent treatments. In real-world clinical practice, patients who had intracranial progressions with stable extracranial lesions after first-/second-generation TKIs treatment tend to perform plasma genotyping or take osimertinib blindly. But the efficacy of osimertinib in those patients according to their T790M mutational status from plasma genotyping has not been explored.

In this real-world study, 25 EGFR-mutated advanced NSCLC patients started osimertinib treatment due to intracranial oligo-progressions after previous EGFR TKI treatment. Among them, 1/3 patients chose to take osimertinib directly without taking any genetic examination and 2/3 patients underwent plasma genotyping. Among patients taking plasma genotyping, 50% of these patients were positive for EGFR T790M mutation, a proportion similar to previous reports.[11]

At data cutoff (Jun 5, 2021), 21/25 (84%) patients with brain progressions achieved systemic disease control. 14/14 (100.0%) patients with evaluable brain lesions achieved intracranial disease control. Among patients with unevaluable brain lesions, 9/11 (81.8%) of them experienced a reduction of their brain lesions. The median PFS for the total population was 8.0 months, and the median iPFS was 14.4 months. Our data confirmed the intracranial efficacy and manageable safety profile of osimertinib in real-world practice, with the CNS DCR and median PFS consistent with previous reports about the CNS efficacy of osimertinib for EGFR-mutated NSCLC after previous TKI treatment[12,13] and no obvious adverse reactions reported.

We found no difference in both PFS and iPFS according to EGFR T790M mutational status in our patients, even after excluding the seven patients who received radiotherapy in combination with osimertinib treatment considering that radiotherapy may interfere with the efficacy of osimertinib (supplementary figure 3). Notably, patients without T790M mutation and patients with unknown T790M mutational status also reached a CNS DCR of 100.0%, and the systemic DCR was 66.7% and 87.5%, respectively. It has been reported that osimertinib showed good efficacy in pretreated EGFRm NSCLC patients with LM regardless of their T790M status.[14,15] In our study, osimertinib displayed optimal efficacy in pretreated patients with BM irrespective of their T790M mutational status from plasma genotyping. Two explanations should be considered. For one thing, the single plasma genotyping may not be able to capture the real mutational status due to the low T790M mutation abundance in the liquid sample and the inherent tumor heterogeneity. Hata A et al reported that, for patients who were re-biopsied after

Table 2. Best Response for Osimertinib Treatment.

Best Response	EGFR T790M Positive	EGFR T790M Negative	EGFR T790M Blind	Total
Evaluable intracerebral lesions				
No. of patients	4	5	5	14
PR	0	2	2	4
SD	4	3	3	10
PD	0	0	0	0
DCR	100%	100%	100%	100%
Unevaluable intracerebral lesions				
No. of patients	4	4	3	11
reduction	4	3	2	9
Stable	0	1	1	2
Extracerebral lesions				
No. of patients	8	9	8	25
PR	1	1	0	2
SD	7	5	7	19
PD	0	3	1	4
DCR	100.0%	66.7%	87.5%	84.0%
Overall lesions				
No. of patients	8	9	8	25
PR	0	2	0	2
SD	8	4	7	19
PD	0	3	1	4
DCR	100.0%	66.7%	87.5%	84.0%

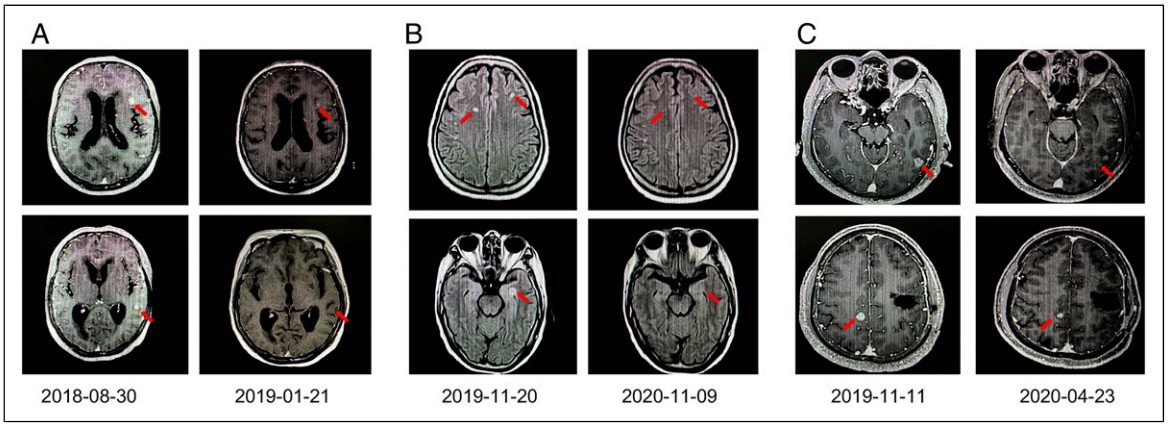

Figure 3. Magnetic resonance imaging brain scans before and after treatment with osimertinib in three patients with partial response. (A) The intracranial response of osimertinib in the patient with T790M; (B) intracranial response of osimertinib in the patient with no T790M; (C) intracranial response of osimertinib in the patient with unknown T790M status.

progression on previous TKI, only 17% were T790M positive within CNS metastases, while 41% in systemic lesions.[16] Another possible explanation is that the intact blood-brain barrier inhibits the penetration of first-/second-generation EGFR-TKIs into the CSF, resulting in the control of extracranial disease but intracranial progression. And osimertinib, which has a greater CNS penetration ability, brought the intracranial progressive lesions under control again.[6] Therefore, no matter whether patients have developed T790M mutation or not, the superior CNS efficacy of osimertinib can provide benefit for patients with intracranial progressions in that situation. Apart from T790M mutation, the intracranial progressions could be attributed to mechanisms such as other EGFR second-point mutations, alternative pathway activation, or histological and phenotypic transformation.[17] The fact that we did not spot any resistance mechanism by plasma genotyping yet spotted the initial sensitizing mutations in our T790M-negative patients (supplementary methods) makes the insufficient intracranial concentration of previous TKIs a more plausible explanation. The observed efficacy of osimertinib

among our patients can further validate our speculation. The median iPFS was longer than median PFS might partly owing to the increase in censored cases who developed extracranial progressions. Or, more likely, the CNS lesions may have been underexposed to previous EGFR TKIs compared with extracranial lesions, resulting in higher response and a longer median iPFS than median PFS. The consistency of clinical outcomes among our patients demonstrated that osimertinib is applicable in such situation irrespective of T790M mutational status from plasma genotyping.

In our study, a patient was found to harbor FGF3/4/9 amplification and KRAS amplification through plasma genotyping after progression on osimertinib. Considering that these mutations had not been spotted in the patient before osimertinib treatment, we thought of the secondary FGF amplification and KRAS amplification, both of which have been proved to be potential resistance mechanisms of osimertinib,[18-21] as the potential causes leading to the progression of the patient. Thus, despite that osimertinib is effective for patients with intracranial oligo-progressions when the resistance mechanism of previous TKI treatment remains unclear, genetic testing is still recommended for patients for it can monitor potential resistance mechanisms dynamically.

Several studies exhibited heterogeneity between CNS metastases and extracranial lesions.[16,22] Maria Colombino et al[23] demonstrated genetic heterogeneity by comparing sequencing of 20 melanomas and paired BM, with some samples harboring BRAF mutations only in the primary and others harboring NRAS mutations only in the BM. Interestingly, one of our patients who started osimertinib treatment without T790M experienced a deterioration of lung lesions while her brain lesion was well-controlled. Subsequent NGS revealed the mutation of EGFR G724S, a potential resistance mechanism of both first-generation TKI and osimertinib.[24,25] The inconsistent responses of intracranial and extracranial lesions in our cases seemingly indicated that the resistance mechanisms were different inside and outside the central nervous system. Signaling networks between the tumor and its metastatic niche may impose differing selective pressures at different metastatic sites, leading to divergent genomic evolution. The CNS, by virtue of its relative isolation compared with other metastatic sites, might be the ideal site for divergent evolution.[26]

There is a limited study comparing the sensitivity of plasma genotyping and CSF genotyping for the mutational profile of CNS lesions. A retrospective study demonstrated that median iPFS and median overall PFS were longer in patients with T790M-positive CSF genotyping than patients with T790M-negative CSF while T790M status in plasma was not associated with response to osimertinib.[27] A study by Li YS et al revealed that CSF is better in reflecting intracranial mutational conditions and could reveal the unique genetic profiles of CNS lesions.[28] It seems that CSF genotyping can better reflect mutational profiles of intracranial lesions than plasma genotyping. However, it is worth noting that all the patients mentioned in the above study had leptomeningeal metastases while our patients were all diagnosed with brain metastases and progressions. A study revealed that the mutation detection rate of CSF circulating tumor DNA (ctDNA) was significantly lower than that from extracranial tissue and plasma for lung cancer patients with brain metastases, which indicated that CSF genotyping is of limited significance in patients with brain parenchymal progressions.[29] Nevertheless, CSF genotyping has its unique value in clarifying the mechanism of intracranial drug resistance. If conditions permit, both plasma genotyping and CSF genotyping should be performed.

Our study did not reveal any factors that can significantly affect the efficacy of osimertinib for NSCLC patients with intracranial oligo-progressions after previous TKIs treatment. It has been reported that in both CSF genotyping and extracranial genotyping, EGFR 19del was associated with better osimertinib response than EGFR L858R.[27,30,31] Our study also showed a statistically significant longer PFS trend for patients with EGFR 19del than EGFR L858R mutation. Although the differential efficacy between 19del and L858R is observed with both first-/second- and third-generation EGFR-TKIs, the recent RELAY study revealed a similar high efficacy of combination therapy with erlotinib plus ramucirumab in patients with L858R and patients with 19del.[32] A consistent PFS benefit between 19del and L858R groups has also been reported in patients receiving erlotinib and bevacizumab,[33] suggesting that the addition of an antiangiogenic agent appears to abrogate the worse outcomes observed in L858 R patients compared with 19del patients when treated with EGFR-TKI monotherapy and the combination regimen would be more suitable for patients with L858R mutation.

There are several limitations to our study. The single-center, retrospective design, and small sample size limit its competence to illustrate the efficacy of osimertinib in this special clinical situation. Additionally, because of the relatively short follow-up time, median OS was not reached. Considering that osimertinib has been approved as first-line therapy for EGFR-mutated NSCLC patients, this study is of more instructive significance for clinicians in developing countries where economic development is limited and osimertinib is temporarily out of reach. But this is still the first study to explore the efficacy of osimertinib according to the T790M mutational status from plasma genotyping for EGFR-mutated advanced NSCLC patients with intracranial oligo-progressions after previous TKI treatment in a real-world setting.

Conclusion

In conclusion, for EGFR-mutated advanced NSCLC patients who progressed on previous TKI with progressive intracranial lesions and stable extracranial diseases, osimertinib can be an effective treatment option regardless of T790M mutational status from plasma genotyping.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The study was approved by Sun Yat-sen University Cancer Center Institutional Review Board (Approval number: B2021-348-01).

Informed Consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Statement of Human and Animal Rights

All procedures in this study were conducted in accordance with the Sun Yat-sen University Cancer Center Institutional Review Board approved protocols (Approval number: B2021-348-01).

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Supplemental Material

Supplemental material for this article is available online.

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