Local control of brain metastases with osimertinib alone in patients with EGFR-mutant non-small cell lung cancer

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Received: 24 August 2022 / Accepted: 21 September 2022 / Published online: 13 October 2022
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Abstract
Purpose Although osimertinib has excellent intracranial activity in metastatic non-small cell lung cancer (NSCLC) with exon 19 deletion or L858R EGFR alterations, measures of local control of brain metastases are less well-reported. We describe lesion-level outcomes of brain metastases treated with osimertinib alone.

Methods We retrospectively reviewed patients with EGFR-mutant NSCLC with untreated brain metastasis measuring ≥ 5 mm at the time of initiating osimertinib. Cumulative incidence of local recurrence in brain (LRiB) was calculated with death as a competing risk, and univariable and multivariable analyses were conducted to identify factors associated with LRiB.

Results We included 284 brain metastases from 37 patients. Median follow-up was 20.1 months. On initial MRI after starting osimertinib, patient-level response was complete response (CR) in 11 (15%), partial response (PR) in 33 (45%), stable disease (SD) in 18 (25%) and progressive disease (PD) in 11 (15%). The 1-year cumulative incidence of LRiB was 14% (95% CI 9.9–17.9) and was significantly different in patients with a CR (0%), PR (4%), and SD (11%; \( p = 0.02 \)). Uncontrolled primary tumor (adjusted hazard ratio [aHR] 3.78, 95% CI 1.87–7.66; \( p < 0.001 \)), increasing number of prior systemic therapies (aHR 2.12, 95% CI 1.49–3.04; \( p < 0.001 \)), and higher ECOG score (aHR 7.8, 95% CI 1.99–31.81; \( p = 0.003 \)) were associated with LRiB.

Conclusions Although 1-year cumulative incidence of LRiB is < 4% with a CR or PR, 1-year cumulative incidence of LRiB is over 10% for patients with less than a PR to osimertinib on initial MRI. These patients should be followed closely for need for additional treatment such as stereotactic radiosurgery.

Keywords Radiation oncology · TKI · NSCLC · SRS · Osimertinib · Radiation

Introduction

Metastatic disease to the brain is common in patients with non-small cell lung cancer (NSCLC), with 15–20% of patients presenting with brain metastases at diagnosis, and up to 40% of patients developing brain metastases during their disease course [1–3]. Patients with epidermal growth factor receptor (EGFR)-mutant lung cancer have been reported to have a significantly higher incidence of brain metastases when compared to EGFR-wild type tumors [4–6].
While surgery and radiation are important local treatment modalities for brain metastases, new systemic therapies have also demonstrated promising intracranial efficacy [7–17]. One example is osimertinib, a tyrosine kinase inhibitor (TKI) targeting EGFR-mutated NSCLC [15–18]. Although osimertinib is now widely used for patients with EGFR-mutant NSCLC brain metastases, it is controversial whether these novel treatments can serve as a replacement for local brain-directed therapies such as radiation. Numerous trials investigating osimertinib have reported intracranial response endpoints [15–18] but lack details regarding the durability of response and lesion-level outcomes.

In our study, we therefore describe longitudinal lesion-level outcomes of brain metastases in patients with EGFR-mutant metastatic NSCLC treated with osimertinib alone to better inform the optimal integration and sequencing of local brain-directed treatments.

**Materials and methods**

**Patient population**

In this institutional review board-approved retrospective study, we identified patients with metastatic EGFR-mutant NSCLC with brain metastases treated with osimertinib alone, with deferral of radiotherapy/radiosurgery, at the Stanford Cancer Center from 2016 to 2021. We included patients with at least one untreated brain lesion with a maximal diameter of 5 mm or larger on MRI at the time of initiating first- or later-line osimertinib. The decision for osimertinib-alone therapy for these patients was made on a case-by-case basis and at a multidisciplinary central nervous system and/or thoracic tumor board. Patients selected for osimertinib-alone therapy were typically asymptomatic with respect to their brain lesions. Patients must have had at least one follow-up brain MRI after the initiation of osimertinib. Patients with leptomeningeal disease were excluded.

**Brain lesion segmentation protocol**

VBrain, an FDA-approved brain tumor segmentation tool, was used to reproducibly identify, track, and measure brain lesions on baseline and follow-up MRI brain scans. The total number of MRIs analyzed with automated segmentation was 282 scans. VBrain has been shown to accurately segment lesions, with a Dice similarity coefficient of 0.70, which measures the overlap between VBrain and medical professionals, and a 93.9% sensitivity for detecting brain lesions with maximal diameter 5 mm or larger [19]. Using axial T1-weighted post-contrast MR image data, VBrain automatically segmented eligible brain metastases for each scan. A tumor trace algorithm then created correspondences between tumors across longitudinal scans. Specifically, a rigid registration was used to map all tumor segments into the same physical coordinates at different timestamps. Metadata including tumor diameter, presence of new lesions, and tumor response assessments were extracted from serial MRI scans. All auto-segmented contours were independently reviewed and verified by radiation oncologists with expertise in treating brain metastases.

**Primary outcomes**

Primary outcomes were initial response using modified RECIST 1.1 criteria [20] and local control of brain metastases. By using a 5 mm minimal diameter threshold for brain lesions, the modified RECIST criteria allowed for the inclusion of additional brain lesions (RANO-BM uses a 10 mm threshold). Comparison between modified RECIST criteria and others such as RANO-BM in evaluating brain metastasis response to systemic therapy show high concordance [21]. Response was categorized as complete (CR), partial (PR), stable disease (SD), or progressive disease (PD) at the time of first follow-up brain MRI per modified RECIST criteria 1.1. Of target lesions (≥ 5 mm), CR was defined as complete disappearance of all lesions, PR was defined as ≥ 30% decrease in diameter, and PD was defined as ≥ 20% increase in diameter. SD was defined as not meeting criteria for CR, PR, or PD. When more than one brain lesion was present, the sum of the diameters of the largest lesions up to a maximum of five lesions total was used. Local recurrence in brain (LRiB) was defined as ≥ 20% increase in the maximum diameter of a brain metastasis on serial imaging.

**Statistical analysis**

The cumulative incidences of LRiB, distant intracranial progression, and extracranial progression were calculated from the start of osimertinib with death as a competing risk and censored at the last imaging follow up. LRiB was calculated on a per-lesion basis, and distant intracranial and extracranial progression were calculated on a per-patient basis. Overall survival (OS) was calculated with Kaplan–Meier from the start of osimertinib. Intracranial progression-free survival was defined as time from the start of osimertinib until date of CNS progression or death. Univariable and multivariable competing risks regression with repeated measures assessed the association between patient and lesion characteristics and LRiB. Variables included in the multivariable model included the number of prior systemic treatments, performance status, whether the primary tumor was controlled or not, and size of the brain metastases. Gray’s test was used to compare the time to local recurrence between patients with an initial response of CR, PR, PD, and SD. A p-value of < 0.05 was considered statistically significant and all p-values were obtained from two-sided tests. All analyses were performed in SAS (SAS Institute Inc, Cary, NC).
Results

Patient, tumor, and treatment characteristics

From 2016 to 2021, 37 patients with 284 untreated brain metastases with a maximal diameter of 5 mm or larger were identified (Table 1). Median age at the time of first brain metastases was 57 years (range 30–90 years). Most (78%) patients were female and had never smoked (84%). Most (65%) had not received systemic therapy prior to osimertinib. Those who received later-line osimertinib were treated previously with earlier-generation TKIs (22%), chemotherapy (22%), and/or immunotherapy (8%). Median time from the diagnosis of brain metastases to the start of osimertinib was 17 days (range 0–2978 days). Median maximal size of untreated brain metastases was 6.9 mm (range 5.0–33.6 mm). The median number of brain metastases was 3 (range 1–43); Almost half (49%) of patients had only 1–2 intracranial lesions 5 mm and larger at the time of osimertinib initiation.

Outcomes

Median time to the first scan assessing response was 7 weeks (range 2.1–17.9 weeks). At the first follow up brain MRI after initiating osimertinib, CR was demonstrated in 11 (15%) patients, PR in 33 (45%) patients, SD in 18 (25%) patients, and PD in 11 (15%) patients. For patients receiving first-line osimertinib, 12%, 50%, 17%, and 12% had CR, PR, SD, PD, respectively.

Median follow-up time for all patients was 20 months (range 1.7–47 months) and the median time on osimertinib was 15 months (range 0.23–50.9 months). Median intracranial progression-free survival was 13.5 months for the entire cohort (range 0.2–50.3 months).

The 1-year cumulative incidence of LRiB was 14% (95% CI 9.9–17.9; Fig. 1). Median time to LRiB was 7.5 months. All local recurrences occurred prior to discontinuation of osimertinib for toxicity or for progression of disease.

For patients receiving first-line osimertinib, the 1-year cumulative incidence of LRiB was 4% (95% CI 1.5–6.9%) and the median time to LRiB was 7 months. The median intracranial progression-free survival was also 13.5 months for patients receiving first-line osimertinib.

In all patients with a CR within the brain, the 1-year cumulative incidence of LRiB was 0%. The 1-year cumulative incidence of LRiB was 4% (95% CI 1.9–7.5) in patients with PR and 11% (95% CI 2.7–25.7) in patients with SD. The time to local recurrence was significantly different between the three groups (Fig. 2; \( p = 0.02 \)). At the

### Table 1 Patient, tumor, and treatment characteristics at time of initiation of osimertinib

| Characteristic                          | N (%)                                                                 |
|-----------------------------------------|-----------------------------------------------------------------------|
| Age (median, years)                     | 57 (range 30–90)                                                     |
| Gender                                  |                                                                       |
| Male                                    | 8 (21.6%)                                                            |
| Female                                  | 29 (78.4%)                                                           |
| Ethnicity                               |                                                                       |
| White                                   | 9 (24.3%)                                                            |
| Hispanic                                | 4 (10.8%)                                                            |
| Asian                                   | 22 (59.5%)                                                           |
| Unknown                                 | 2 (5.4%)                                                             |
| ECOG score                              |                                                                       |
| 0–1                                     | 31 (83.8%)                                                           |
| 2+                                      | 6 (16.2%)                                                            |
| Smoking history                         |                                                                       |
| Never                                   | 31 (83.8%)                                                           |
| Former                                  | 6 (16.2%)                                                            |
| Pack Years (median)                     | 0 (range 2.5–80)                                                    |
| Current                                 | 0 (0%)                                                               |
| Prior tumor controlled\(^a\)            |                                                                       |
| Yes                                     | 4 (10.8%)                                                            |
| No                                      | 33 (89.2%)                                                           |
| Extracranial organs involved\(^b\)      |                                                                       |
| 0                                       | 5 (13.5%)                                                            |
| 1–2                                     | 23 (62.2%)                                                           |
| 3+                                      | 9 (24.3%)                                                            |
| Number of prior systemic therapies      |                                                                       |
| 0                                       | 24 (64.9%)                                                           |
| 1–3                                     | 12 (32.4%)                                                           |
| 4+                                      | 1 (2.7%)                                                             |
| Prior TKI                               |                                                                       |
| Yes                                     | 8 (21.6%)                                                            |
| No                                      | 29 (78.4%)                                                           |
| Prior chemotherapy                      |                                                                       |
| Yes                                     | 8 (21.6%)                                                            |
| No                                      | 29 (78.4%)                                                           |
| Prior immunotherapy                     |                                                                       |
| Yes                                     | 3 (8.1%)                                                             |
| No                                      | 34 (91.9%)                                                           |
| Prior surgery for brain metastases      |                                                                       |
| Yes                                     | 3 (8.1%)                                                             |
| No                                      | 34 (91.9%)                                                           |
| Prior radiation therapy for brain metastases\(^c\) |                                      |
| Yes                                     | 5 (13.5%)                                                            |
| SRS                                     | 4 (10.8%)                                                            |
| WBRT                                    | 1 (2.7%)                                                             |
| No                                      | 27 (73%)                                                             |
| Size of untreated brain metastases\(^d\) (median, mm) | 6.9 (range 5.0–33.6)                                               |
| <2 cm                                   | 280 (98.6%)                                                          |

\(^a\) Yes for any intracranial setting

\(^b\) Excluding patients with CR, PR, SD, PD

\(^c\) SRS, surgery, WBRT, whole brain radiation therapy

\(^d\) Medical treatment in Table 1
time of last follow up, 0% (0/13), 6% (12/197), and 17% (5/29) of the lesions had locally recurred in patients who had a CR, PR, and SD, respectively.

On univariable analysis, uncontrolled primary tumor (adjusted hazard ratio [aHR] 3.78, 95% CI 1.87–7.66; p < 0.01), increasing number of prior systemic therapies before osimertinib (aHR 2.12, 95% CI 1.49–3.04; p < 0.01), and ECOG score > 1 (aHR 7.8, 95% CI 1.99–31.81; p < 0.01) were associated with LRiB. These factors remained significant after controlling for total number of intracranial lesions (Table 2). Patient age, size of brain metastases, and total number of intracranial lesions were not significantly associated with LRiB.

Median OS was 27.2 months (95% confidence interval [CI] 21.1–39). The 1-year cumulative incidences of distant intracranial and extracranial progression were 39% (95% CI 22.7–54.5), and 49% (95% CI 32.5–64.8), respectively. Of patients who experienced LRiB, 80% and 86% also experienced distant intracranial progression and extracranial progression, respectively, at the time of LRiB.

Of the ten patients who underwent salvage SRS to twelve lesions for LRiB, the 1-year cumulative incidence of local failure after salvage SRS was 0%. One patient ultimately underwent whole brain radiotherapy 13 months after salvage SRS for local failure and distant intracranial failure.

**Discussion**

Osimertinib has shown excellent intracranial response in patients with metastatic EGFR-mutant NSCLC [16, 17, 22, 23]. Our study provides additional insight into the local recurrence outcomes of over 200 individual brain lesions followed over hundreds of brain MRIs in patients with EGFR-mutant NSCLC treated with osimertinib at a single institution. We found that local control with osimertinib alone is good, with only 14% of brain metastases progressing at 1 year, which is comparable to local control rates of around 90% with SRS alone [24, 25]. Additionally, 90% patients who underwent salvage SRS for LRiB in our study had their brain lesions locally controlled. Intracranial progression reflected extracranial disease behavior, with risk of local recurrence associated with primary tumor control, lines of systemic therapy received, and performance status. Additionally, we found that the initial intracranial response corresponded to local control in our patient cohort, with no further progression in those lesions that responded completely to osimertinib. By comparison, 11% of those lesions that remained stable without a partial or complete response to osimertinib later progressed at 1 year.

The importance of radiation therapy in treating intracranial disease in patients with EGFR-mutated NSCLC was demonstrated in the setting of first-generation TKIs such as erlotinib. A multi-institutional retrospective study by Magnuson et al. found that upfront stereotactic radiosurgery (SRS) or whole brain radiation therapy (WBRT) in addition...
to TKIs (mainly erlotinib) was associated with significantly improved survival, despite more patients in the SRS cohort having larger and symptomatic brain metastases. Interestingly, although the patients in the WBRT group had less favorable prognosis with lower GPA scores and a greater number of metastases, survival for patients undergoing upfront WBRT was significantly higher than the TKI alone group [26]. Similarly, a meta-analysis including 13 studies showed that upfront radiation therapy in addition to TKIs including erlotinib, gefitinib, or icotinib, had significantly improved overall survival and intracranial progression-free survival compared to EGFR-TKI alone [27].

Although these previous studies have shown that first- or second-generation EGFR-TKIs can reduce the risk of CNS progression when compared to chemotherapy, preclinical studies have shown that these drugs have limited blood–brain-barrier penetration [22, 28–30]. In contrast to these first- and second-generation EGFR-TKIs, osimertinib has been shown to have excellent brain distribution in pre-clinical studies, which has translated into superior intracranial control [16, 17, 22, 23]. In a multi-institutional retrospective study of 147 patients with EGFR- or ALK-positive NSCLC, Thomas et al. found no significant differences in time to progression, intracranial progression, or treatment failure between patients receiving CNS-penetrant TKIs alone (including osimertinib) versus upfront radiation plus TKI, suggesting that local radiation may be deferred in appropriately selected patients [31]. However, a higher percentage of patients in the group receiving radiation therapy plus TKI were symptomatic from their brain metastases and more likely to have received steroids before treatment. Despite these unfavorable prognostic factors in the radiation group, outcomes did not differ, suggesting that upfront CNS radiation may have provided some additional disease control among patients with more aggressive CNS disease features. In a smaller single institution retrospective study, radiation therapy prior to starting osimertinib for patients with progressing brain lesions did not significantly improve the time to treatment failure, progression free survival, or overall survival compared to patients who received osimertinib alone [32]. Patients who received osimertinib alone on this study also had smaller brain lesions. Despite the retrospective nature of these studies, with imbalances between baseline patient characteristics and selection bias, these preliminary results suggest that local brain-directed therapies may be judiciously deferred in a favorable cohort of patients.

However, it remains difficult to discern which patients or what specific brain metastases may safely be followed with close surveillance imaging versus those who may benefit from upfront SRS. At many institutions, such decisions are often made through a multi-disciplinary approach. Although lesion-level outcome data can help to further guide treatment decision-making, the intracranial efficacy of osimertinib is mostly reported as overall response rate or progression-free survival. For example, the AURA study used RECIST 1.1 to define overall response rate as the percentage of patients with at least one surveillance scan showing CR or PR, with another confirmatory surveillance scan 4 weeks later.
metastases on osimertinib alone, over 10% of metastases have excellent response of untreated intracranial metastases. Although patients with EGFR-mutant NSCLC with brain metastases, where the probability of CR/PR is higher with osimertinib in the larger lesions can likely be extrapolated to smaller lesions. Though confirmation is necessary we believe that our results generalize to everyday clinical practice. Further studies including smaller brain lesions can help to improve the tool to measure brain metastases over multiple scans. Further, despite a high proportion of patients obtaining an initial PR, some intracranial lesions still experienced LRiB, highlighting the importance of close follow-up and consideration of earlier local therapy for those high-risk lesions. There are several limitations to this retrospective study. First, although our institution treats a high volume of patients with EGFR-mutant NSCLC, this is still a small study at a single institution, which limits power and generalizability. Another limitation includes exclusion of brain metastases smaller than 5 mm. Although multiple studies have reported that patients with larger brain lesions experience worse local control after radiation therapy alone, our study did not show a significant association between the size of brain metastases and LF [24, 33, 34]. This may be due to excluding lesions smaller than 5 mm in our study and/or to a difference in the effects of osimertinib on larger brain metastases compared to SRS. We excluded these smaller lesions due to the intra- and interobserver variability in measuring small brain metastases [35] and because RECIST includes only lesions larger than 1 cm [20]. To reduce the impact of measurement variability, we used an FDA-approved tool to measure brain metastases over multiple scans. Further studies including smaller brain lesions can help to improve the generalizability of our results to everyday clinical practice. Though confirmation is necessary we believe that our results in the larger lesions can likely be extrapolated to smaller lesions where the probability of CR/PR is higher with osimertinib given the more limited disease burden.

Conclusion

Although patients with EGFR-mutant NSCLC with brain metastases have excellent response of untreated intracranial metastases on osimertinib alone, over 10% of metastases will progress locally at 1 year. Patients with worse performance status, high number of previous systemic therapies, and patients with uncontrolled primaries with osimertinib initiation were more likely to experience local progression of brain metastases. Further studies should be done to validate the risk factors identified from our retrospective study and to identify the brain metastases at risk for local failure to guide optimal intracranial management in these patients.

Author contributions CH: Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing—Original Draft, Writing—Review & Editing, Visualization, Project administration. VQ: Investigation, Data Curation, Writing—Original Draft, Writing—Review & Editing, J-YW: Writing—Original Draft, Writing—Review & Editing, RyE: Formal Analysis, Writing—Review & Editing, Y-CC, P-LC, C-HL, J-TL: Formal Analysis, Resources, Writing—Review & Editing, GL, MH-G, HW, JN, KR, MD, SN: Writing—Review & Editing, Visualization. SS: Conceptualization, Methodology, Writing—Original Draft, Writing—Review & Editing, NM: Conceptualization, Methodology, Validation, Writing—Original Draft, Writing—Review & Editing, Supervision, Project administration. EP: Conceptualization, Methodology, Validation, Data Curation, Writing—Original Draft, Writing—Review & Editing, Supervision, Project administration.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest For authors Yu-Cheng Chang, Po-Lin Chiang, Chih-Hung Liang, Jen-Tang Lu, a US patent is granted for Vysioneer software, and these authors also have Vysioneer Inc. stocks. For author Scott Soltys: Zap Surgical, Inc.—Speaker Honoraria; Novocure, Inc.—Research Funding; Accuray, Inc.—Consultant. For author Millie Scott Soltys: Zap Surgical, Inc.—Speaker Honoraria; Novocure, Inc.—Research Funding; Accuray, Inc.—Consultant. For author Melanie Hayden-Gephart: Merck, Genentech, CellSight, Novartis, Abbvie, United Therapeutics, Varian, Verily, Celgene. For author Melanie Hayden-Gephart: U54CA261717. All other authors have no conflicts of interest.

Ethics approval This study did not require ethics approval.

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