Aumolertinib challenge as an optional treatment in advanced non small-cell lung cancer after osimertinib failure with epidermal growth factor receptor-sensitive mutation: A case series

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Abstract. Osimertinib, as the first third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), has been recommended universally as the priority front-line therapeutic for advanced non-small cell lung cancer (NSCLC) carrying EGFR-sensitive mutations. However, patients inevitably acquire drug resistance to osimertinib. Aumolertinib is the second third-generation EGFR-TKI and has been similarly approved as a first-line treatment agent. The present study reports the cases of 3 patients who were challenged with aumolertinib after osimertinib failure. All 3 patients achieved a partial remission. The progression-free survival periods following aumolertinib were 10.0, 11 and 9.0 months (at the time of writing the study). Although the patient in case 2 succumbed to an intracerebral hemorrhage due to hypertension, aumolertinib remained effective as a treatment in cases 1 and 3. The present case series suggests the use of aumolertinib challenge as an optional treatment for patients with metastatic NSCLC harboring EGFR-sensitive mutations after osimertinib failure. The therapeutic strategy of switching from osimertinib to aumolertinib is worth exploring further in the near future.

Introduction

Currently, molecular targeted therapies have been recommended as standard treatments for patients with non-small cell lung cancer (NSCLC) carrying driver gene alterations, such as epidermal growth factor receptor (EGFR) mutations. As the first third-generation EGFR tyrosine kinase inhibitor (TKI), osimertinib is generally preferred as the first-line standard of care therapeutic for untreated EGFR-mutated (ex19del or L858R) advanced NSCLC due to its superior efficacy and tolerability (1). Despite a median progression-free survival (mPFS) time of 18.9 months, patients inevitably develop acquired drug resistance to osimertinib after the initial clinical benefit (2). However, only a small number of osimertinib-resistant mechanisms have been clarified, including MET 14 exon-skipping mutation (15%) and EGFR C797S mutation (7%) (3). To date, most osimertinib-resistant mechanisms have not been identified. Hence, there is a huge unmet medical need to develop novel therapeutic strategies to tackle the resistance to osimertinib.

Since 2019, China has continuously developed domestic third-generation EGFR TKI agents, including aumolertinib (formerly almonertinib; HS-10296) by Jiangsu Hansoh Pharmaceutical Group Co., Ltd. and furmonertinib by Shanghai Allist Pharmaceutical Technology Co., Ltd., as well as D0316 by Betta Pharma Co., Ltd. (4-6). In 2020, the Chinese Society of Clinical Oncology (CSCO) guidelines approved aumolertinib as a second-line treatment for patients with advanced NSCLC and T790M mutation. In 2021, CSCO guidelines recommended aumolertinib as a first-line treatment for patients with advanced NSCLC and EGFR-sensitive mutations (7). Recently, some reports have emerged on the alternatives for overcoming resistance to osimertinib, such as use of brigatinib alone or in combination with cetuximab (8,9). Also, CSCO guidelines on NSCLC recommended furmonertinib (another third-generation EGFR-TKI in China) to treat advanced T790M-positive NSCLC after failure of other EGFR-TKI treatment. However, furmonertinib was not listed into the catalogue of drugs for Basic National Medical Insurance of China in 2021. By contrast, aumolertinib was covered in the catalogue. Thus, aumolertinib was administered by Jiujiang University Affiliated Hospital (Jiujiang, China) in an attempt to treat several patients with osimertinib-resistant advanced NSCLC. The present study reports the details of 3 patients who developed resistance to osimertinib and favorably responded to subsequent aumolertinib treatment.

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Case report

Case 1. A 70-year-old female patient was admitted to Jiujiang University Affiliated Hospital in January 2021, with complaints of a cough and expectoration for 2 months. The patient had a persistent dry cough but no fever, night sweats or hemoptysis. The medical history included type 2 diabetes and Parkinson's disease for 11 years, with no history of smoking. No superficial lymphadenopathy was palpable, and no abnormal breath sounds were heard. The patient's Eastern Cooperative Oncology Group (ECOG) performance score was 0 points (10). Chest computed tomography (CT) imaging upon admission reported a large mass (3.6x3.1 cm) occupying the inferior lobe of the right lung and an accompanying small pleural effusion (Fig. 1A). Positron emission tomography/CT imaging showed no bone metastases at the time of diagnosis, and no metastases were noted during a brain magnetic resonance imaging (MRI) examination. The definite pathological diagnosis was confirmed as invasive lung adenocarcinoma via percutaneous lung puncture. High-throughput sequencing revealed an EGFR exon 21 mutation (L858R). The Tumor-Node-Metastasis (TNM) stage was IVB (cT4N0M1c) (American Joint Committee on Cancer TNM eighth version) (11).

The CSCO NSCLC guidelines (2021 version) have recommended both osimertinib and aumolertinib as first-line treatments for patients with stage IV NSCLC harboring EGFR-sensitive mutations (12). However, aumolertinib is not included under Chinese basic medical insurance, whereas osimertinib is. At 2 weeks post-admission, the patient was started on osimertinib at the standard dose of 80 mg once daily. After 2 months, the first efficacy evaluation revealed that the lung lesion had decreased in size markedly, and the pleural effusion had disappeared, indicating that partial remission (PR) had been achieved (Fig. 1B). Thereafter, efficacy was regularly assessed every 1-2 months. After 5 months of osimertinib treatment, however, a chest CT scan revealed that the primary lung foci appeared significantly larger, and the pleural effusion had increased in size again (Fig. 1C). The clinical efficacy result was assessed as progressive disease (PD), suggesting the existence of osimertinib resistance. Furthermore, EGFR gene mutant status was examined in a peripheral blood sample, revealing an EGFR exon 20-T790M mutation. Due to the frailty and advanced age of the patient, chemotherapy plus antiangiogenic therapy was refused.

After sufficient communication, the patient was treated with oral aumolertinib (110 mg per day) beginning in July 2021. Unexpectedly, a substantial PR response was achieved again after 2 months (Fig. 1D). However, at this time, the patient experienced mild acute pancreatitis, and aumolertinib therapy was paused. The patient recovered completely from the acute pancreatitis within 2 weeks. In September 2021, the patient complained of mild chest tightness and chest discomfort. Chest CT imaging revealed that the primary lung foci and pleural effusion had progressed again (Fig. 1E), and aumolertinib therapy was re-instated. The patient achieved PR once again (Fig. 1F). To date, the patient is continuing on aumolertinib treatment and stable disease has been recorded. The first and second PR periods for aumolertinib were 2.0 and 8 months, respectively. The total PFS time (defined as the time from the initial treatment of aumolertinib to disease progression) was 10 months (at the time of writing this study).

Case 2. In May 2018, a 64-year-old female patient presented to Jiujiang University Affiliated Hospital due to dizziness for 2 weeks. The patient complained of mild nausea and vomiting, tiredness and headaches. No pulmonary symptoms were documented, such as a cough, expectoration, dyspnea or chest pain. The patient had a history of hypertension for >10 years and no history of smoking. Chest CT showed two solid masses in the upper and lower lobes of the right lung, with a maximum diameter of 3.5x2.2 cm (Fig. 2Aa and b). Next, a plain and enhanced MRI examination was performed, which revealed multiple brain metastases in the bilateral cerebral hemisphere, right cerebellar hemisphere, basal ganglia and thalamus (Fig. 2Ba-c). Color-ultrasound revealed that the left supraclavicular lymph nodes were enlarged, with a diameter of 7-9 mm. Spine and pelvic MRI found multiple osteolytic bone lesions in the sternum, thoracic vertebrae, lumbar vertebrae and ilium (data not shown). Bronchoscopy was performed, revealing a small mass in the opening of the right intermediate bronchus. The biopsy revealed poorly differentiated adenocarcinoma, and genetic testing showed an EGFR 19 delete mutation. According to the TNM staging system, the patient had stage IVB disease.

According to the NSCLC guideline of CSCO, the patient received osimertinib monotherapy (80 mg) once daily from 2 weeks post-admission. Concurrently, anti-resorptive therapy using 4 mg zoledronic acid was administered every 4 weeks. After 2 weeks, the patient reported that the symptoms of dizziness and light-headedness were resolved. Subsequent multiple reviews showed a great reduction in tumor volume of the primary pulmonary and brain lesions (data not shown), indicating a PR response. However, 19 months later, the patient was admitted to the emergency room with a numb face and aphasia. Reflexes were decreased in the lower extremities. Chest CT did not confirm pulmonary lesion progression (Fig. 2Ca and b), but brain MRI depicted extensive small tumor infiltrations (Fig. 2Da-c). The EGFR gene testing of a peripheral blood sample showed a T790M mutation. PD was indicated and the patient refused the recommended chemotherapy.

After communicating fully with family members, the patient received aumolertinib treatment (110 mg daily) from January 2020. After 1 month, language functions were considerably recovered. A regular evaluation of efficacy was planned every 1-2 months. As the patient's compliance was not very good, the first evaluation of efficacy was performed 5 months after beginning aumolertinib therapy. Chest CT imaging revealed that the pulmonary cancer lesion was stable (Fig. 2Ea and b), while brain MRI showed that the extensive small infiltrations of the brain had greatly diminished (Fig. 2Fa-c). From this point, efficacy was assessed every 1-2 months; however, the patient succumbed to an intracerebral hemorrhage in December 2020. At that time, brain CT and MRI revealed that the intracerebral hemorrhage was in the basal ganglia in the left hemisphere, but no intracranial space-occupying lesions were clearly detected, with the exception of a few obscure small infiltrations of metastases. The metastases remained in PR status. Notably, the blood pressure

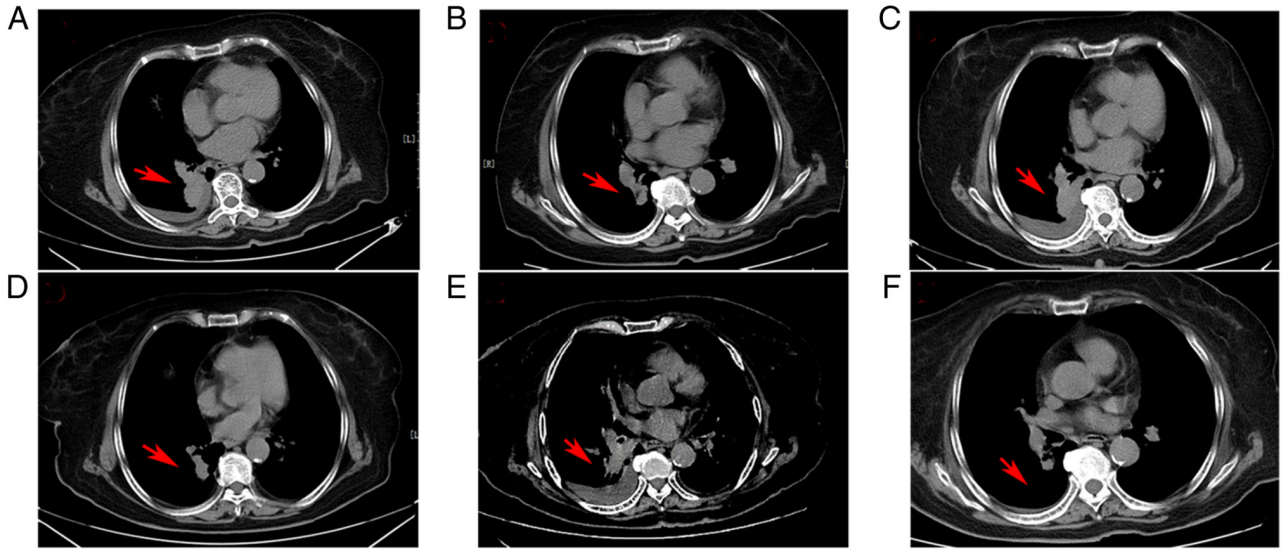

Figure 1. Radiological images showing the changes in patient 1 during the total treatment period. (A) The initial computed tomography scan showed a tumor (3.6x3.1 cm) in the inferior lobe of the right lung at diagnosis (January 2021). (B) The tumor decreased to 2.8x1.8 cm after osimertinib treatment for 2 months (April 2021). (C). The tumor increased to 3.7x3.2 cm after osimertinib for 5 months (July 2021). (D) The tumor shrunk to 1.5x1.2 cm after aumolertinib for 2 months (September 2021). (E) The tumor enlarged to 3.7x3.2 cm after aumolertinib interruption for 2 weeks due to mild acute pancreatitis (September 2021). (F) The lesion disappeared after resuming aumolertinib treatment for 6 weeks (November 2021). The tumor location is indicated by the red arrow.

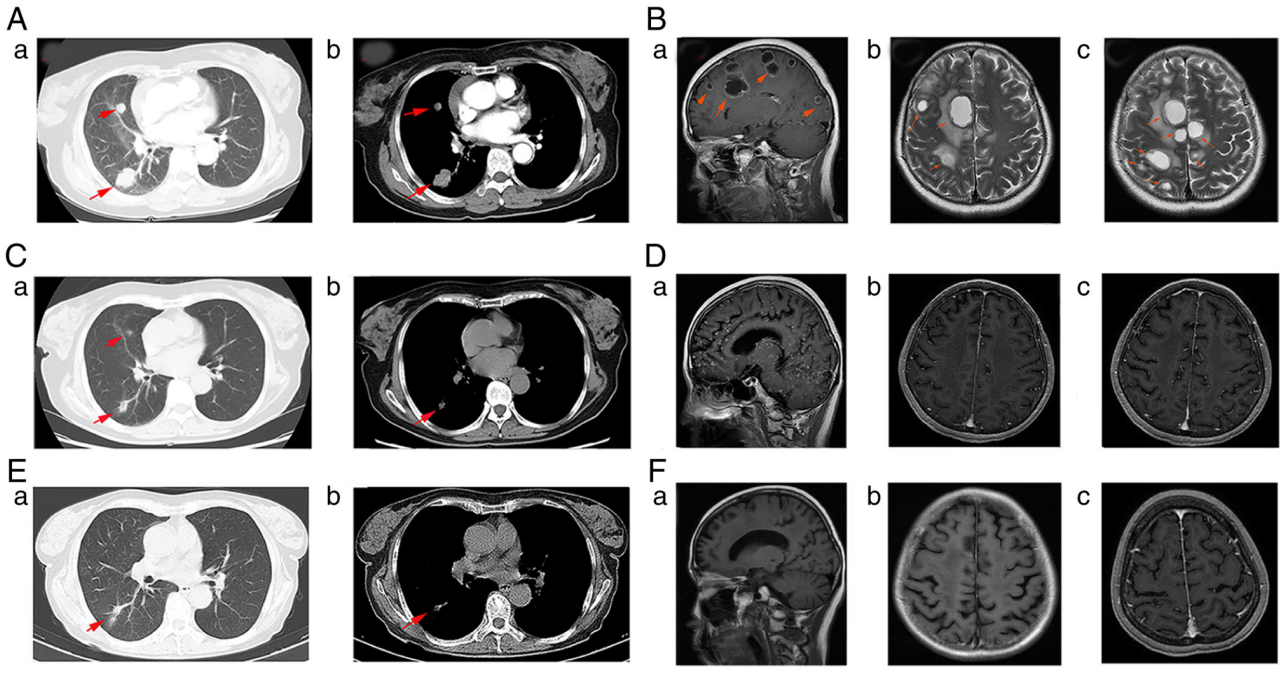

Figure 2. Radiological images showing the changes in patient 2 during the total treatment period. (Aa and b) A chest CT scan showed two lesions in the upper and lower lobes of the right lung, with a maximum diameter of 3.5x2.2 cm at diagnosis (May 2018). (Ba-c) Craniocerebral MRI scans revealed multiple brain metastases at diagnosis (May 2018); (Ca and b) Chest CT confirmed partial remission of the pulmonary lesion (0.6x0.5 cm) after osimertinib treatment for 19 months (January 2020). (Da-c) Brain MRI depicted extensive small infiltrations by tumors after osimertinib treatment for 19 months (January 2020). (Ea and b) A chest CT scan showed that the pulmonary lesion was stable after aumolertinib treatment for 5 months (0.5x0.5 cm) (June 2020). (Fa-c) Brain MRI scan confirmed reduced diffused brain metastases after aumolertinib treatment for 5 months (June 2020). The tumor location is indicated by the red arrow. CT, computed tomography; MRI, magnetic resonance imaging.

before admission to the hospital was 180/110 mmHg and the patient experienced agitation for 2 min before lapsing into a coma. These symptoms strongly indicated that the intracerebral hemorrhage was not from metastasis but from the poor control of hypertension. The PFS time following aumolertinib was 11 months.

Case 3. A 75-year-old female patient was referred to Jiujiang University Affiliated Hospital in January 2020. The patient complained of a cough and expectoration with right-sided chest pain for 3 weeks, with no history of smoking. A chest CT examination showed a large lesion in the right upper lung with a diameter of 4.8x4.1 cm and lymphadenopathy in the

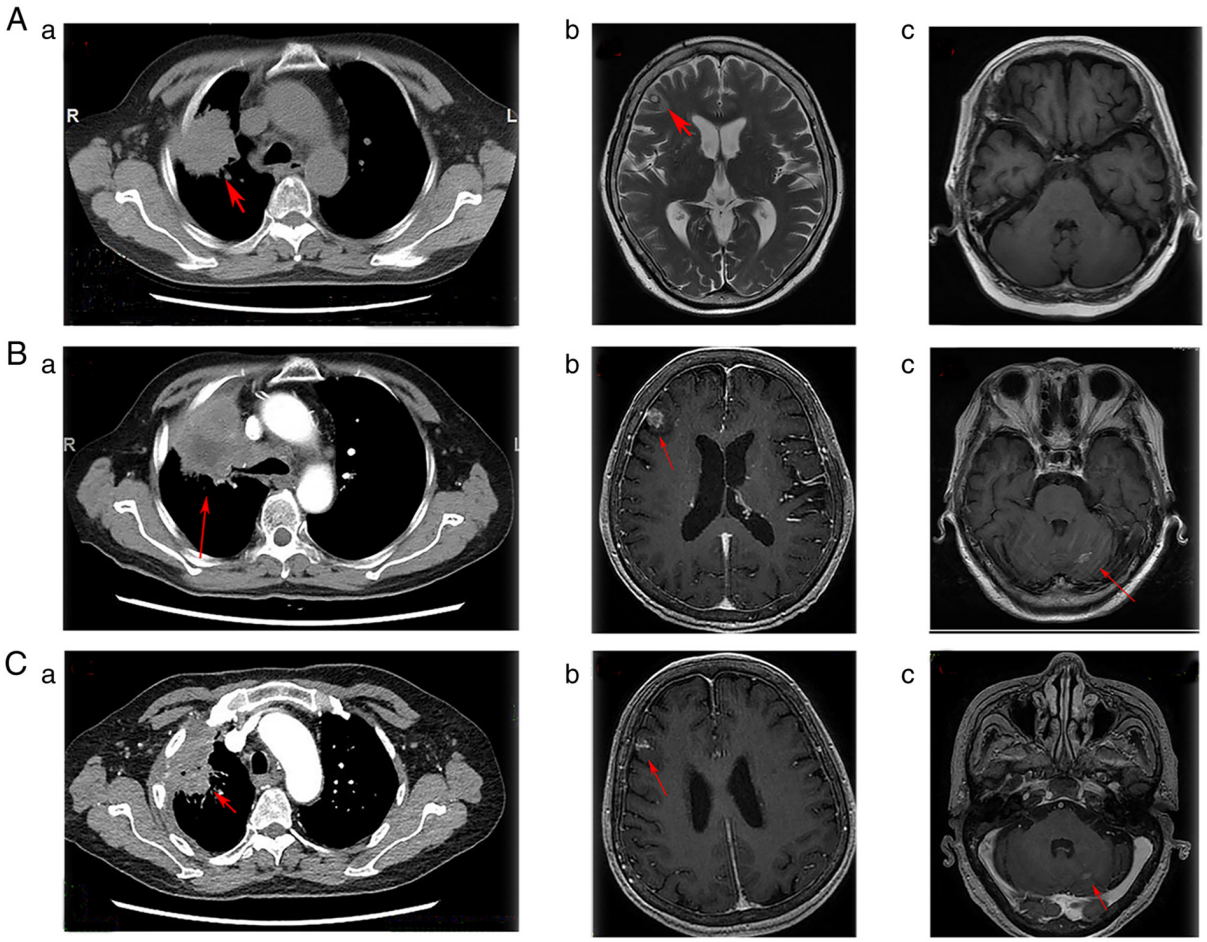

Figure 3. Radiological images showing the changes in patient 3 during the total treatment period. (Aa) A chest CT scan showed a right upper lung lesion (4.8x4.1 cm) at diagnosis (January 2020). (Ab-c) Brain MRI scans showed a lesion in the right frontal lobe of brain (0.8x1.0 cm) at diagnosis (January 2020). (Ba) The lung lesions enlarged (6.7x5.3 cm) after osimertinib treatment for 18 months (August 2021). (Bb-c) The right frontal lobe lesion increased to 1.4x1.1 cm and a new lesion appeared in the left cerebellum (0.8x0.6 cm) after osimertinib treatment for 18 months (August 2021). (Ca) Chest CT scans revealed the lung lesion decreased to 4.6x2.5 cm after aumolertinib treatment for 4 months (December 2021). (Cb-c) Brain MRI scans showed both brain lesions decreased to 0.9x0.6 cm and 0.4x0.3 cm, respectively (December 2020). The tumor location is indicated by the red arrow. CT, computed tomography; MRI, magnetic resonance imaging.

mediastinum (Fig. 3Aa). The brain MRI findings demonstrated a solid lesion in the right frontal lobe (0.8x1.0 cm) (Fig. 3Ab and c). A CT-guided percutaneous fine-needle aspiration biopsy was performed, which confirmed invasive adenocarcinoma with an EGFR 21 exon L858R mutation based on next-generation sequencing (NGS). The clinical TNM stage was IVB (cT4N3M1c), and the ECOG score was 1 point. The patient began osimertinib treatment (80 mg daily) in January 2020 and, 1 month later, the clinical pulmonary symptoms were greatly relieved. A regular review was performed every 3 months thereafter, and the results of cranial MRI and thoracic/abdominal CT examinations showed a PR response (data not shown).

However, in August 2021, the patient experienced increased chest pain and a cough, with mild dizziness. Chest CT imaging demonstrated that the right upper lung lesion had increased to 6.7x5.3 cm (Fig. 3Ba). Brain MRI confirmed that the right frontal lobe lesion had grown to 1.4x1.1 cm, and a novel lesion measuring 0.8x0.6 cm had appeared in the left cerebellum (Fig. 3Bb and c). The imaging examination indicated a response result of PD. The patient underwent a second percutaneous fine-needle aspiration biopsy, which again revealed invasive adenocarcinoma and an EGFR exon 20 T790M mutation based on NGS. After communicating with their family, the patient declined to accept chemotherapy. Subsequently, the patient started to receive aumolertinib treatment (110 mg daily) in August 2021. The scheduled evaluation of efficacy was every 1-2 months, but the compliance of the patient was poor and therefore the first efficacy assessment was only accepted 4 months after starting aumolertinib treatment. A chest CT examination showed that the pulmonary lesion had decreased to 4.6x2.5 cm (Fig. 3Ca). Similarly, cranio-cerebral MRI imaging revealed that the right frontal lobe lesion had reduced significantly in size to 0.8x0.5 cm, and the left cerebellum lesion to 0.4x0.3 cm (Fig. 3Cb). The clinical efficacy was assessed as PR. Following this, the patient accepted the efficacy evaluation regularly every 1-2 months. The patient has continued to receive aumolertinib treatment to date. The PFS time following aumolertinib was 9 months (at the time of writing this study).

Methods

H&E and immunohistochemistry staining. The needle lung biopsy was fixed for 6 h with 10% neutral formalin at 35-37˚C.

Routine sampling, dehydration and embedding were performed, followed by sectioning into 4-μm thick samples, which were stained using hematoxylin and eosin at room temperature for 1 h, and assessed under a light microscope. Immunohistochemical staining was also performed.

Sequencing. The Tiangen paraffin-embedded tissue DNA extraction kit (cat. #DP304-02; Tiangen Biotech Co., Ltd.) was used to extract DNA from the sample to be sequenced. A Qseq1 Bioanalyzer was used to verify the quality/integrity of the processed samples. The type of sequencing was 150 bp for length and paired-end for direction. The NextSeq 500/550 Mid Output v2 kit (300 cycles; cat. #FC-404-2003; Berry Genomics, Co., Ltd.) was used in conjunction with a sequencer to complete the high-throughput sequencing process and obtain sample sequence information. The loading concentration of the final library was 1.7 pM measured by Micro quantitative detector. The sequencing data analysis process is as follows: i) Data quality control: fastp, version 0.23.0 (https://github.com/OpenGene/fastp); ii) data comparison: bwa, version 0.7.17 (http://bio-bwa.sourceforge.net); iii) variation detection: GATK, version 3.8 (https://software.broadinstitute.org/gatk); iv) variation annotation: SnpEff, version 5.0 (https://pcingola.github.io/SnpEff/); v) Report generation: self-built software (http://www.yunkanghealth.com/technology).

Discussion

As the first third-line EGFR TKI, osimertinib has been universally approved as the first-line treatment for patients with advanced NSCLC carrying EGFR-sensitive mutations. The FLAURA study showed that the PFS time following use of osimertinib as a front-line therapy was 18.9 months (2). However, acquired drug resistance occurs eventually and inevitably. Currently, only a minority of patients with osimertinib-resistant NSCLC have the opportunity to receive savolitinib treatment against MET 14 exon-skipping mutations (13). Platinum-containing chemotherapy remains the most common treatment for most osimertinib-resistant patients (14). Recently, a retrospective study compared osimertinib plus bevacizumab vs. chemotherapy plus bevacizumab in patients with EGFR-mutant NSCLC after the failure of osimertinib, and concluded the superiority of osimertinib plus bevacizumab over chemotherapy plus bevacizumab (7.0 vs. 4.9 months mPFS time) (15). In addition, in certain case reports, erlotinib together with bevacizumab has been reported to overcome osimertinib resistance (16). The present study reported the switch to aumolertinib treatment in patients with advanced NSCLC harboring EGFR-sensitive mutations who were resistant to osimertinib.

Aumolertinib is the second third-generation EGFR TKI and breaks the monopoly situation on the use of osimertinib worldwide. The APOLLO study enrolled 244 patients with EGFR T790M-positive NSCLC who received aumolertinib treatment. The overall response rate (ORR) and disease control rate (DCR) were 68.9 and 93.4%, respectively, and the mPFS time was 12.4 months. For the 23 patients with assessable central nervous system (CNS) metastases, the CNS-ORR and CNS-DCR were 60.9 and 91.3%, respectively. These results indicate that aumolertinib is an effective third-generation EGFR TKI for patients with EGFR T790M-positive advanced NSCLC after disease progression following first- and second-generation EGFR TKI therapy (17). In the mouse model of NSCLC brain and spinal cord metastases, aumolertinib easily penetrates the blood-brain barrier and inhibits brain and spinal cord metastases (18). In the AENEAS study, aumolertinib, as a first-line treatment for locally advanced or metastatic EGFR-mutated NSCLC, achieved a PFS time of 19.3 months, which is marginally higher than the time of 18.9 months achieved with osimertinib in the FLAURA study (4). A recent network meta-analysis showed that in terms of brain metastases, third-generation EGFR-TKIs showed obvious superiority, with aumolertinib and osimertinib both optimally prolonging PFS time in patients with brain metastases (19). These studies offer strong support for the potent anticancer activity of aumolertinib against EGFR-mutant NSCLC cells, in particular for brain metastases.

In a case report by Shen *et al* (20), almonertinib overcame osimertinib resistance associated with the L718Q mutation in a patient with metastatic NSCLC. Wu *et al* (21) and Zhang *et al* (22) reported successful treatment with aumolertinib after osimertinib-induced interstitial lung disease and cardiotoxicity. These results suggested a potential agent for reversing drug osimertinib-resistance and indicated a better safety profile for aumolertinib compared with that for osimertinib. In the present case reports, the three patients developed osimertinib resistance with T790M mutation and without other additional genetic mutations, which indicated no available targeted therapy. Therefore, aumolertinib was employed to treat the patients with osimertinib-resistant advanced NSCLC. Encouragingly, the 3 patients achieved PFS times of 10^{+}, 11 and 9^{+} months. Although the patient in case 2 succumbed to hypertension-induced intracerebral hemorrhage, aumolertinib remained effective in the three cases, with a mPFS time of >9 months. Notably, the patient in case 1 had an episode of acute pancreatitis, from which they quickly recovered and which did not occur again during the period following aumolertinib treatment, indicating the lack of connection of aumolertinib with the onset of acute pancreatitis.

The possible mechanisms of a successful challenge with aumolertinib in osimertinib-resistant NSCLC may, in part, be ascribed to the following factors. One is that aumolertinib carries lower half maximal inhibitory values for T790M and L858R mutations, and T790M and Del 19 mutations, respectively, than osimertinib (i.e., 0.29 vs. 0.46 nmol/l, and 0.21 vs. 0.29 nmol/l) (23). The other is that aumolertinib may partly overcome the drug resistance of osimertinib in advanced NSCLC (21). Finally, the mean plasma concentration of aumolertinib (110 mg/day) is slightly higher than that of osimertinib (80 mg/day) (155.5 vs. 138.98 ng/ml) (24). Additionally, for patients with advanced NSCLC and EGFR exon 20 insertion mutations, aumolertinib has been reported to achieve the PFS time of 10.0 months (25), while osimertinib leads to a mere mPFS time of 2.3 months (26). Therefore, to some extent, aumolertinib and osimertinib belong to completely different EGFR TKI categories despite being parts of the same third-generation EGFR TKI group.

In conclusion, in the present report, aumolertinib challenge is described as an optional treatment after osimertinib failure for patients with EGFR-sensitive mutations. The limitation of the present study is its small sample size, and the conclusions

of this retrospective study need to be further explored and validated.

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Availability of data and materials

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

Authors' contributions

JD designed and revised the manuscript. XD drafted the manuscript and analyzed the patient data. ZL and YS acquired the raw data, obtained the medical images, advised on patient treatment and analyzed patient data as the patients' medical intern and primary medical oncologist, respectively. XD, JD, ZL and YS confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was granted by the Medical Ethics Committee of Jiujiang University Affiliated Hospital (Jiujiang, China; approval no. jjuhmer-a-2020-01).

Patient consent for publication

Patients from cases 1 and 3 gave written consent for the publication of the current study. The son of the patient from case 2 gave written consent for publication of the current study.

Competing interests

The authors declare that they have no competing interests.

References

1. He J, Huang Z, Han L, Gong Y and Xie C: Mechanisms and management of 3rd-generation EGFR-TKI resistance in advanced non-small cell lung cancer (Review). Int J Oncol 59: 90, 2021.
2. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, *et al*: Osimertinib in Untreated EGFR-Mutated Advanced non-small-cell lung cancer. N Engl J Med 378: 113-125, 2018.
3. Schmid S, Li JJN and Leighl NB: Mechanisms of osimertinib resistance and emerging treatment options. Lung Cancer 147: 123-129, 2020.
4. Lu S, Dong X, Jian H, Chen J, Chen G, Sun Y, Ji Y, Wang Z, Shi J, Lu J, *et al*: AENEAS: A randomized phase III trial of aumolertinib versus gefitinib as first-line therapy for locally advanced or metastaticnon-small-cell lung cancer with EGFR Exon 19 Deletion or L858R Mutations. J Clin Oncol: Sep 20, 2022 (Epub ahead of print).
5. Deeks ED: Furmonertinib: First Approval. Drugs 81: 1775-1780, 2021.
6. Jian H, Wang K, Cheng Y, Ding L, Wang Y, Shi Z, Zhang L, Wang Y and Lu S: Phase I trial of a third generation EGFR mutant-selective inhibitor (D-0316) in patients with advanced non-small cell lung cancer. Oncologist 27: 163-e213, 2022.
7. Lv W, Cheng H, Shao D, Wei Y, Zhu W, Wu K, Jiang W, Hu L, Sha Z, Zhong B and Pei X: Treatment patterns and survival of patients with advanced non-small cell lung cancer guided by comprehensive genomic profiling: Real-World single-institute study in China. Front Oncol 11: 630717, 2021.
8. Chang Y, Liu S, Jiang Y, Hua L and Wen L: Effective treatment of pulmonary adenocarcinoma harboring triple EGFR mutations of L858R, T790M, cis-G796s/cis-C797s by osimertinib, brigatinib, and bevacizumab combination therapy: A case report. Respir Med Case Rep 36: 101582, 2022.
9. Wang Y, Han R, Zhu M, He T and He Y: Case report: Durable response to the combination of brigatinib and cetuximab plus icotinib in a NSCLC patient harboring EGFR L858R-T790M-cis-G796S and L718Q resistance mutations following progression with osimertinib. Front Oncol 12: 875313, 2022.
10. Yang F, Markovic SN, Molina JR, Halfdanarson TR, Pagliaro LC, Chintakuntlawar AV, Li R, Wei J, Wang L, Liu B, *et al*: Association of sex, age, and eastern cooperative oncology group performance status with survival benefit of cancer immunotherapy in randomized clinical trials: A systematic review and meta-analysis. JAMA Netw Open 3: e2012534, 2020.
11. Chansky K, Detterbeck FC, Nicholson AG, Rusch VW, Vallieres E, Groome P, Kennedy C, Krasnik M, Peake M, Shemanski L, *et al*: The IASLC lung cancer staging project: External validation of the revision of the TNM stage groupings in the eighth edition of the TNM classification of lung cancer. J Thorac Oncol 12: 1109-1121, 2017.
12. Fang C, Liu T, Liang W, Feng S, Su Z, Tang H, Huang H and Chen Z: Clinical pharmacist participation in selecting and dosing targeted drugs for a patient with ALK-positive non-small cell lung cancer: A case report. Ann Transl Med 9: 1488, 2021.
13. Ma P, Huang R, Gu Y, Fang Y, Wu X, Chen DS, Zhang HW, Gao W and Shu Y: Savolitinib monotherapy exerted significant benefit in a non-small cell lung cancer patient with osimertinib resistance harboring primary EGFR L858R mutation and MET amplification: A case report. Anticancer Drugs: Aug 10, 2022 (Epub ahead of print).
14. Lim JU: Overcoming osimertinib resistance in advanced non-small cell lung cancer. Clin Oncol (R Coll Radiol) 33: 619-626, 2021.
15. Cui Q, Hu Y, Cui Q, Wu D, Mao Y, Ma D and Liu H: Osimertinib rechallenge with bevacizumab vs. chemotherapy plus bevacizumab in EGFR-Mutant NSCLC patients with osimertinib resistance. Front Pharmacol 12: 746707, 2021.
16. Satoh H and Kagohashi K: Response to erlotinib and bevacizumab combination therapy after acquired resistance to osimertinib in patients with non-small cell lung cancer. Anticancer Drugs 33: 320-322, 2022.
17. Lu S, Wang Q, Zhang G, Dong X, Yang CT, Song Y, Chang GC, Lu Y, Pan H, Chiu CH, *et al*: Efficacy of Aumolertinib (HS-10296) in Patients With Advanced EGFR T790M+ NSCLC: Updated post-national medical products administration approval results from the APOLLO registrational trial. J Thorac Oncol 17: 411-422, 2022.
18. Zhang Y, Zhang Y, Niu W, Ge X, Huang F, Pang J, Li X, Wang Y, Gao W, Fan F, *et al*: Experimental study of almonertinib crossing the blood-brain barrier in EGFR-Mutant NSCLC brain metastasis and spinal cord metastasis models. Front Pharmacol 12: 750031, 2021.
19. Yang F, Zhang W, Shang X, Liu N, Ma X, Qin J, Zhang Y, Liu Y and Wang X: Comparison of the efficacy and safety of first-line treatments based on clinicopathological characteristics for patients with advanced epidermal growth factor receptor mutated non-small-cell lung cancer: A systematic review and network meta-analysis. Crit Rev Oncol Hematol 177: 103760, 2022.
20. Shen G, Shi L, Tian X, Huang D, Chen H, Gao C, Shen X and Zhang H: Case report: Response to almonertinib in a patient with metastatic NSCLC resistant to osimertinib due to acquired EGFR L718Q Mutation. Front Pharmacol 12: 731895, 2021.

21. Wu L, Zhong W, Li A, Qiu Z, Xie R, Shi H and Lu S: Successful treatment of EGFR T790M-mutant non-small cell lung cancer with almonertinib after osimertinib-induced interstitial lung disease: A case report and literature review. Ann Transl Med 9: 950, 2021.
22. Zhang Q, Liu H and Yang J: Aumolertinib effectively reduces clinical symptoms of an EGFR L858R-Mutant non-small cell lung cancer case coupled with osimertinib-induced carditoxicity: Case report and review. Front Endocrinol 13: 833929, 2022.
23. Yang JC, Camidge DR, Yang CT, Zhou J, Guo R, Chiu CH, Chang GC, Shiah HS, Chen Y, Wang CC, *et al*: Safety, efficacy, and pharmacokinetics of almonertinib (HS-10296) in pretreated patients With EGFR-Mutated advanced NSCLC: A multicenter, open-label, phase 1 trial. J Thorac Oncol 15: 1907-1918, 2020.
24. Li Y, Meng L, Ma Y, Li Y, Xing X, Guo C and Dong Z: Determination of osimertinib, aumolertinib, and furmonertinib in human plasma for therapeutic drug monitoring by UPLC-MS/MS. Molecules 27: 4474, 2022.
25. Deng Y, Yang C, Liu W, Cai S and Guo X: Aumolertinib-based comprehensive treatment for an uncommon site of EGFR exon 20 insertion mutations with multiple metastases non-small cell lung cancer: A case report. Anticancer Drugs 33: 406-412, 2022.
26. Yang GJ, Li J, Xu HY, Sun Y, Liu L, Li HS, Yang L, Zhang Y, Li GH and Wang Y: Osimertinib for Chinese advanced non-small cell lung cancer patients harboring diverse EGFR exon 20 insertion mutations. Lung Cancer 152: 39-48, 2021.