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Successful salvage therapy using high-dose furmonertinib (AST2818) for non–small-cell lung cancer after Osimertinib resistance: a case report

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Osimertinib, the third generation of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, responds well to advanced non–small-cell lung cancer (NSCLC) with the EGFR T790M mutation. However, resistance to osimertinib would inevitably occur. We report a case of an advanced NSCLC patient after osimertinib resistance who was successfully treated by high-dose furmonertinib (AST2818) at 160 mg. The patient initially received the GCP regimen for 11 months and displayed partial response. The patient received osimertinib 80 mg at the time of progression with a stable clinical and radiological response lasting only 7 months. Subsequently, she was commenced on furmonertinib 160 mg once daily. After 2 weeks of furmonertinib, the patient's tumor was markedly smaller on a follow-up chest CT scan, and her respiratory symptoms also improved. What shocked us was that after a month's re-examination of the cranial MRI, the intracranial lesions wholly disappeared. This report provides a case of the successful rescue of osimertinib-resistant NSCLC patients by oral administration of high-dose furmonertinib 160 mg daily, providing a new treatment option for osimertinib-resistant patients. *Anti-Cancer Drugs* 33: 768–772 Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Lung cancer has the highest morbidity and mortality worldwide, and lung adenocarcinoma is the most common pathological subtype. Mutations in the gene encoding epidermal growth factor receptor (EGFR) can be detected in up to 50% of East-Asian patients and 10–15% of Caucasian patients with non–small-cell lung cancer (NSCLC) [1,2]. Therefore, targeted therapy for managing NSCLC with EGFR mutations is of epoch-making significance. EGFR tyrosine kinase inhibitors (TKIs) have shown promising curative effects in NSCLC patients. However, drug resistance is inevitable even in patients benefiting from EGFR-TKIs. Different mechanisms of acquired resistance to second-generation EGFR TKIs and first-generation have been reported, and acquired EGFR T790M mutation is the main reason [2]. Osimertinib is an oral, third-generation, irreversible EGFR-TKI that is effective against both EGFR T790M mutation or other sensitizing mutations [3]. However, how to solve the problem of drug resistance to osimertinib is still a significant challenge.

Furmonertinib mesylate (AST2818), the third generation of EGFR-TKIs, developed by Allist Pharmaceuticals, has demonstrated promising clinical efficacy in patients with minimal toxicity [4]. In a multi-center, single-arm phase IIb study (NCT03452592), the confirmed objective response rate (ORR) and the disease control rate (DCR) were 74% and 94%, respectively [4]. The high efficacy of furmonertinib may be related to the fact that both EGFR T790M mutation and other sensitive mutations can be irreversibly suppressed by furmonertinib and its metabolites (AST5902) [4,5]. It is worth mentioning that no apparent dose-toxicity relationship was observed, and clinical data have demonstrated that furmonertinib is effective in the central nervous system (CNS) [4,5].

Here, we report a case of an advanced NSCLC patient after osimertinib resistance who was successfully treated by high-dose furmonertinib (AST2818) at 160 mg. This report provides some enlightenments for overcoming osimertinib resistance.

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Case presentation

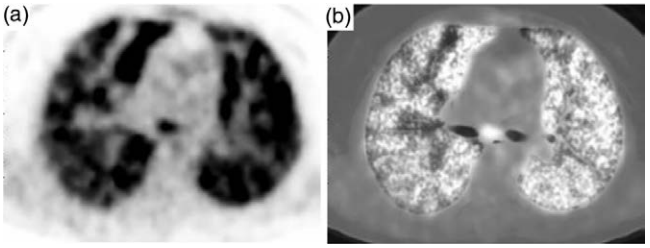
A 53-year-old woman with no smoking history presented to our hospital because of multiple lung nodules revealed on a chest computed tomography. PET/computed tomography (PET/CT) examination showed abnormally increased fluorodeoxyglucose (FDG) metabolism in the left lower lobe mass, diffuse nodules of varying sizes in both lungs, bilateral clavicle area, mediastinum, and both hilum structures have high FDG metabolism (Fig. 1). She was diagnosed with left lung adenocarcinoma (size 3.1 × 3.1 cm), invasion of the hilum, mediastinum, supraclavicular lymph node, and diffuse metastasis to both lungs (cT2aN3M1; stage IV). Capture-based targeted sequencing performed on formalin-fixed paraffin-embedded samples of lung lesions indicated the presence of EGFR exon 19 deletion (p.S752_I759del), with mutation frequencies of 17.7%. She was treated with a first-line GCP regimen (gefitinib 250 mg orally once every day combined with carboplatin area under the curve five and pemetrexed 500 mg/m^2 in a 3-week cycle for up to four cycles, followed by gefitinib maintenance) for 11 months and displayed partial response (Fig. 2). At the time of progression, the number of small nodules in both lungs increased significantly; however, the size of the left lower lung lesion did not increase significantly. Subsequent liquid biopsy on peripheral blood confirmed the original EGFR exon 19 deletion in addition to an acquired T790M in exon 20. Subsequently, the patient received osimertinib 80 mg with a stable clinical and radiological response lasting only 7 months (Fig. 2). Eventually, she experienced rapid disease progression, manifested as diffuse brain and lung metastases, accompanied by the aggravation of her symptoms, including cough, dizziness, and headache. To alleviate the symptoms of brain metastases, whole-brain radiotherapy was used. The next-generation sequence on peripheral blood subsequently showed the loss of T790M mutation and exon 19 deletion. Furmonertinib achieved good results after osimertinib resistance was reported at a domestic academic conference. Thereafter, she was commenced on high-dose furmonertinib 160 mg daily. After 2 weeks of furmonertinib, the patient's tumor was markedly smaller on a follow-up chest CT scan, and her respiratory symptoms also improved (Fig. 3). What shocked us was that after a month's re-examination of the cranial MRI, the intracranial lesions wholly disappeared (Fig. 4). Although she received whole-brain radiotherapy, we believe that targeted drugs furmonertinib have played a key role. The patient's disease remained stable at her last follow-up in December 2021 by treating furmonertinib 160 mg at once daily for 3 months.

Discussion

After osimertinib resistance, we innovatively used a double dose of furmonertinib, successfully relieved the patient's symptoms and lung lesions, and even completely relieved the patient's brain lesions. This provides a successful case for clinical treatment of osimertinib resistance and has brought new lights. It is worth mentioning that both osimertinib and furmonertinib are third-generation EGFR TKIs targeted at EGFR T790M mutation. In this case, the patient's T790M mutation and exon 19 deletion loss after osimertinib resistance, but we managed to reverse the patient's condition with a high dose of furmonertinib. The underlying mechanisms need further investigation. One other thing that needs to be emphasized is that we used a double dose of furmonertinib. This might be related to the patient's favorable outcomes.

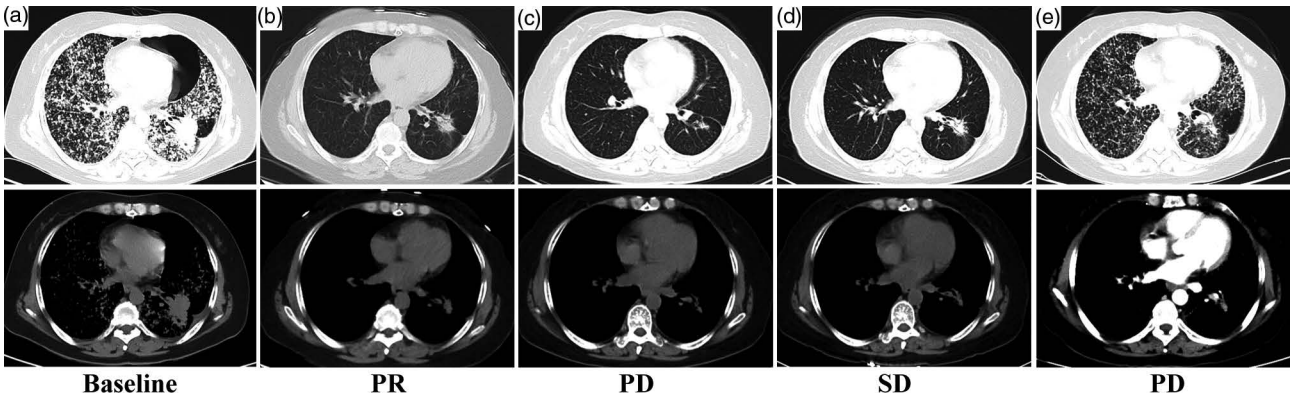
There have been many reports on the mechanism of osimertinib resistance, roughly divided into EGFR mutation-related and EGFR mutation unrelated [3]. The primary mechanism of resistance associated with EGFR mutation is that EGFR acquires additional mutations that break the binding of osimertinib through allosteric/conformational transition changes in the binding site. EGFR exon 20 C797S mutation is the most common EGFR resistance mutation in patients treated with osimertinib that disrupts the cysteine 797 binding site osimertinib relies on [3]. The main resistance mechanisms unrelated to EGFR mutation are activation of abnormal bypass channels or abnormal downstream signaling [6]. In addition, the transformation to small cell lung cancer

Fig. 1



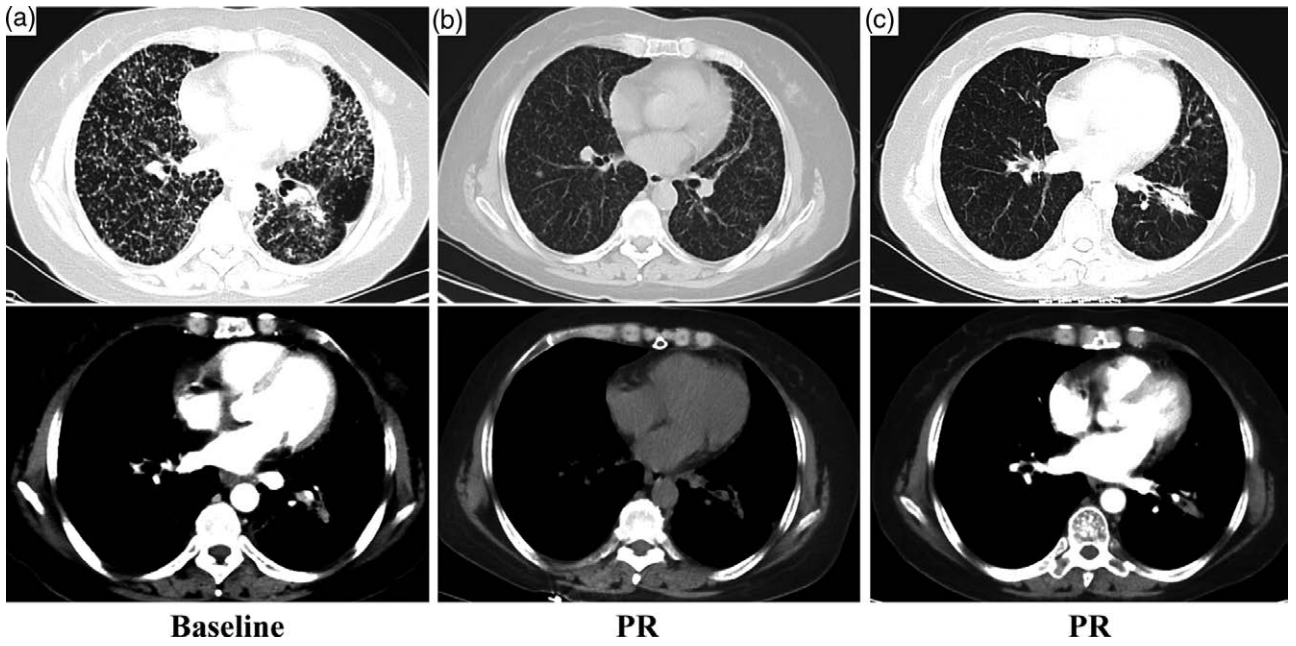
PET-CT examination showed abnormally increased FDG metabolism in the left lower lobe mass, diffuse nodules of varying sizes in both lungs, bilateral clavicle area, mediastinum, and both hilum structures have high FDG metabolism. FDG, fluorodeoxyglucose.

Fig. 2



Computed tomography (CT) scans of the primary lung mass at treatment milestones. The CT images of the primary lung mass at baseline before the initiation of the GCP regimen (a), at the evaluation of PR after one month of GCP regimen (b), at the evaluation of PD after 11 months of GCP regimen (c), at the assessment of SD after one month of osimertinib (d), and the evaluation of PD after 7 months of Osimertinib (e). PR, partial response; SD, stable disease; PD, progressive disease.

Fig. 3



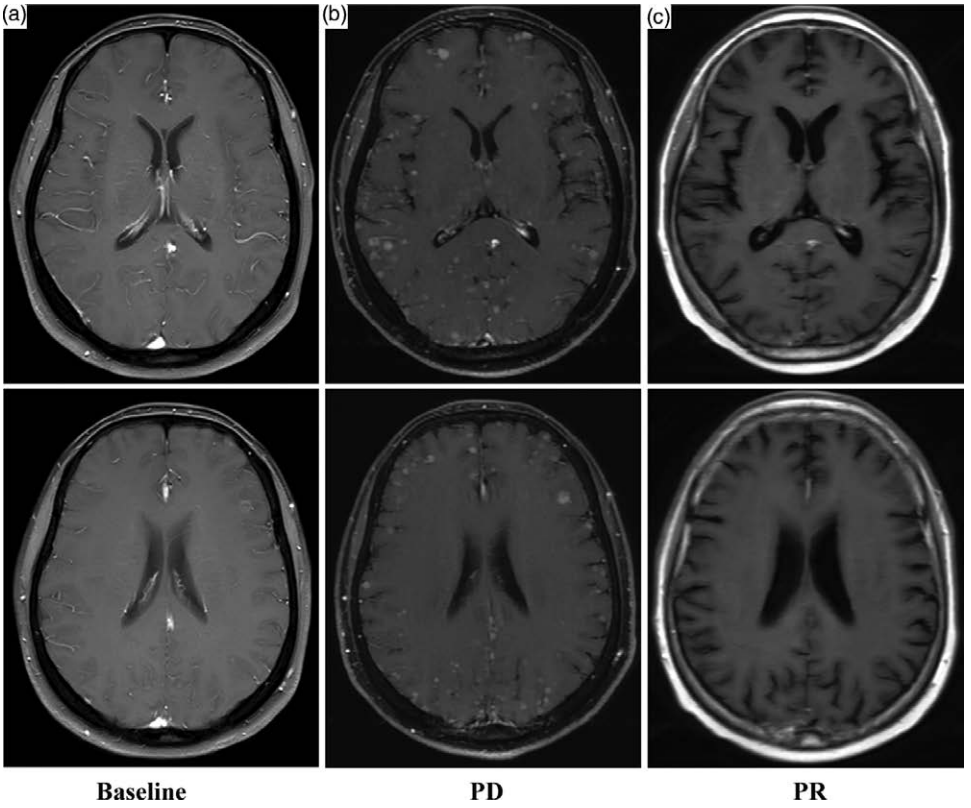
The CT images of the primary lung mass at baseline before the initiation of the furmonertinib (a), at the evaluation of PR after one month of furmonertinib (B), and the evaluation of PR after three months of furmonertinib (c). PR, partial response.

is also one of the mechanisms of osimertinib resistance [6]. Mesenchymal epithelial transition factor amplification was the most common resistance mechanism unrelated to EGFR in patients treated with osimertinib [7]. In this case, the efficacy of the high-dose furmonertinib in the patient after osimertinib resistance may be related to these mechanisms.

Furmonertinib is an effective third-generation EGFR TKIs for resistance with T790M or activating mutations with L858R and exon 19 deletions [8]. In patients with NSCLC with the EGFR T790M mutation, furmonertinib has shown strong efficacy [4]. Furmonertinib's recommended dosage is 80 mg which is administered orally once daily until intolerable toxicity or disease progression. It is worth mentioning that no apparent dose-toxicity relationship was observed [5].

In a phase 2 study, 160 mg of osimertinib was administered daily in patients with brain metastases from NSCLC with

Fig. 4



MRI of the patient's brain after 11 months of GCP regimen (a), at the evaluation of PD after 7 months of osimertinib (b), and the evaluation of PR after one month of furmonertinib (c). PR, partial response; PD, progressive disease.

EGFR T790M mutation; the intracranial ORR was 55.0% in the brain metastasis cohort (BLOOM; NCT02228369) [9]. However, another prospective study reported that the brain metastasis response rate of 80 mg of osimertinib against RT-naive CNS metastasis from T790M-positive NSCLC was 66.7% was higher compared with the ORR 55.0% of BLOOM [10]. This suggests that even though the current dose of osimertinib (80 mg) was increased and the CSF concentrations and blood of osimertinib were increased, no better effect was found. In this report, after oral administration of high-dose furmonertinib, the brain lesions disappeared utterly. High-dose furmonertinib achieved such good results requiring further research, such as whether it is related to high blood solubility and related to the primary active metabolite of furmonertinib (AST5902) parent furmonertinib both could penetrate into the brain [5].

Currently, the patient remains under treatment in a stable condition. It is to be noted that the metabolism of furmonertinib is mainly through CYP3A4, which produces the active desmethyl metabolite AST5902 and other metabolites. Therefore, we should avoid the combination of furmonertinib with CYP3A4 inhibitors/inducers [8].

Even though our report lacks clinical experiments to prove our findings, this study provides a successful clinical case for treating osimertinib-resistant patients with NSCLC, which may become a new potential treatment option. The underlying mechanisms need further investigation.

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Conflicts of interest

There are no conflicts of interest.

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