CASE REPORT

Triple-Dose Furmonertinib for Leptomeningeal Metastases in Advanced *EGFR L858R*-Mutated Lung Adenocarcinoma: A Case Report

Furmonertinib em Dose Tripla no Tratamento de Metástases Leptomeníngeas em Adenocarcinoma do Pulmão Avançado com Mutação EGFR L858R: Relato de Caso

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All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization: Hong Wu, Yuan Tian, Hui Wang. Writing – original draft preparation: Hong Wu. Visualization: Hong Wu, Lei Li, Jing Yang. Writing – review and editing: Yuan Tian, Hui Wang. Supervision: Hui Wang. All authors read and approved the final manuscript.

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ABSTRACT

Leptomeningeal metastases (LM) are a devastating complication of non-small cell lung cancer (NSCLC), particularly in patients with epidermal growth factor receptor (*EGFR*) mutations. Despite the success of EGFR tyrosine kinase inhibitors (TKIs), central nervous system (CNS) progression remains common and associated with poor outcomes due to limited drug penetration. We report a 73-year-old woman with *EGFR L858R*-mutated NSCLC who developed LM after multiple lines of therapy, including gefitinib, osimertinib, chemotherapy, anti-angiogenic therapy, and radiotherapy. Treatment with high-dose furmonertinib (240 mg daily) combined with bevacizumab resulted in symptom relief and additional survival. Remarkably, her overall survival exceeded six years from initial diagnosis. This case highlights the potential role of dose-escalated furmonertinib as salvage therapy in LM after osimertinib resistance and underscores the importance of sequential and multimodal management in advanced *EGFR*-mutant NSCLC.

RESUMO

As metástases leptomeníngeas (ML) constituem uma complicação devastadora do carcinoma do pulmão de não pequenas células (CPNPC), particularmente em doentes com mutações do recetor do fator de crescimento epidérmico (EGFR). Apesar do sucesso dos inibidores da tirosina-quinase do EGFR (TKI), a progressão no sistema nervoso central (SNC) continua a ser frequente e associa-se a um prognóstico desfavorável, em grande parte devido à limitada penetração dos fármacos no SNC. Apresentamos o caso de uma mulher de 73 anos, com CPNPC portador da mutação EGFR L858R, que desenvolveu ML após múltiplas linhas terapêuticas, incluindo gefitinib, osimertinib, quimioterapia, terapêutica antiangiogénica e radioterapia. O tratamento com furmonertinib em dose elevada (240 mg/dia), em associação com bevacizumab, resultou em alívio sintomático e prolongamento adicional da sobrevivência. Notavelmente, a sobrevivência global ultrapassou seis anos desde o diagnóstico inicial. Este caso ilustra o potencial papel do furmonertinib em escalonamento de dose como terapêutica de resgate em ML após resistência ao osimertinib e sublinha a importância de uma abordagem sequencial e multimodal no tratamento do CPNPC avançado com mutação do EGFR.

Keywords:
Adenocarcinoma of Lung/drug therapy; Adenocarcinoma of Lung/genetics; Carcinoma, Non-Small-Cell Lung/drug therapy; Carcinoma, Non-Small-Cell Lung/genetics; ErbB Receptors/genetics; Furmonertinib; Meningeal Neoplasms/secondary

Palavras-chave:
Adenocarcinoma do Pulmão/genética; Adenocarcinoma do Pulmão/tratamento farmacológico; Carcinoma Pulmonar de Células não Pequenas/genética; Carcinoma Pulmonar de Células não Pequenas/tratamento farmacológico; Furmonertinib; Neoplasias Meníngeas/secundárias; Receptores ErbB/genética

INTRODUCTION

Leptomeningeal metastases (LM) represent one of the most challenging forms of CNS progression in lung cancer. NSCLC patients with *EGFR* mutations are at a higher risk of LM compared to EGFR wild-type cases, with an incidence approaching 9%.[1,2] Historically, LM was associated with a median survival of less than one year, even with intrathecal chemotherapy, whole-brain radiotherapy (WBRT), or systemic chemotherapy.[3]

Third-generation EGFR-TKIs, especially osimertinib, have improved CNS control. However, LM progression remains a critical barrier, with limited effective treatment options after osimertinib resistance.[4,5] Furmonertinib, a third-generation EGFR-TKI with favorable CNS penetration, has shown encouraging efficacy in both clinical trials and real-world studies, particularly at higher doses.[6] Nevertheless, detailed case reports describing its use in *EGFR L858R*-mutated NSCLC with LM remain scarce.

We present a patient with *EGFR L858R*-mutated lung adenocarcinoma who survived more than six years after initial diagnosis, including additional survival following LM managed with high-dose furmonertinib and bevacizumab.

CASE REPORT

A 73-year-old nonsmoking woman was admitted to the thoracic surgery department in October 2018 with complaints of chest and back pain. She underwent video-assisted thoracoscopic left upper lobectomy with mediastinal lymph node dissection. Intraoperatively, a 5×4×4 cm mass with ill-defined margins and visceral pleural indentation was observed in the left upper lobe. Postoperative pathology confirmed invasive adenocarcinoma with visceral pleural invasion, and one of seven lymph nodes was positive for metastasis. Molecular testing revealed an *EGFR exon 21 L858R* mutation, and the patient was diagnosed with left lung adenocarcinoma, staged as T2bN1M0 (stage IIB).

Following surgery, the patient received adjuvant gefitinib starting in November 2018. She remained on gefitinib until January 2022, during which regular follow-up demonstrated no evidence of recurrence or metastasis.

In October 2023, she presented again with recurrent chest and back pain. PET-CT revealed mediastinal and hilar lymphadenopathy together with widespread skeletal metastases, indicating postoperative recurrence (Fig. 1).

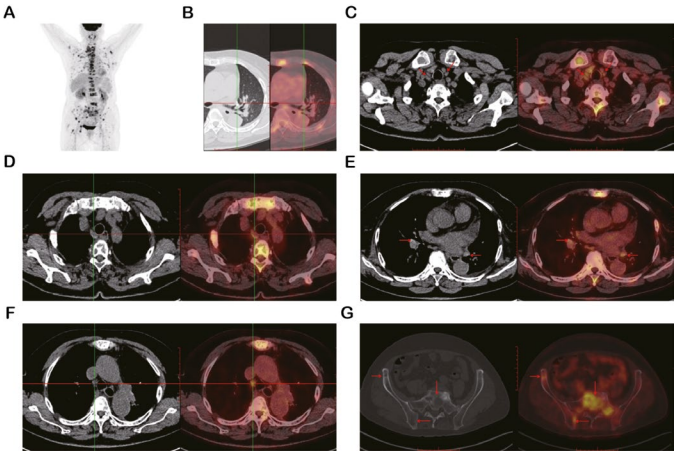

Figure 1 **PET-CT findings suggestive of widespread lymphatic and skeletal metastases**

(**A**) PET-CT demonstrates multiple hypermetabolic lesions involving lymph nodes and bones throughout the body. (**B**) No abnormal FDG uptake detected at the previous surgical site. (**C**) Increased FDG uptake in right paratracheal lymph nodes (SUVmax 4.3). (**D**) Hypermetabolic activity in upper paratracheal lymph nodes (SUVmax 3.8). (**E**) Bilateral hilar lymph nodes with elevated FDG uptake (SUVmax 4.5). (**F**) Marked uptake in lower paratracheal lymph nodes (SUVmax 6.2). (**G**) High FDG uptake in the sacrum, indicative of osseous metastasis (SUVmax 7.2).

She was started on osimertinib 80 mg daily, administered from October 2023 to March 2024, along with palliative radiotherapy to the T2–T3 vertebrae (30 Gy in 10 fractions). Follow-up computed tomography (CT) scans showed partial regression of nodal disease, but progressive left pleural effusion developed (Fig. 2). The patient experienced chest tightness and dyspnea and underwent thoracentesis, followed by intrapleural chemotherapy to control malignant effusion.

From March to December 2024, she received a total of 12 cycles of pemetrexed- and cisplatin-based chemotherapy combined with bevacizumab, followed by maintenance therapy. Imaging demonstrated stable disease in the mediastinum and hilum and a reduction in pleural effusion compared with previous assessments (Fig. 2).

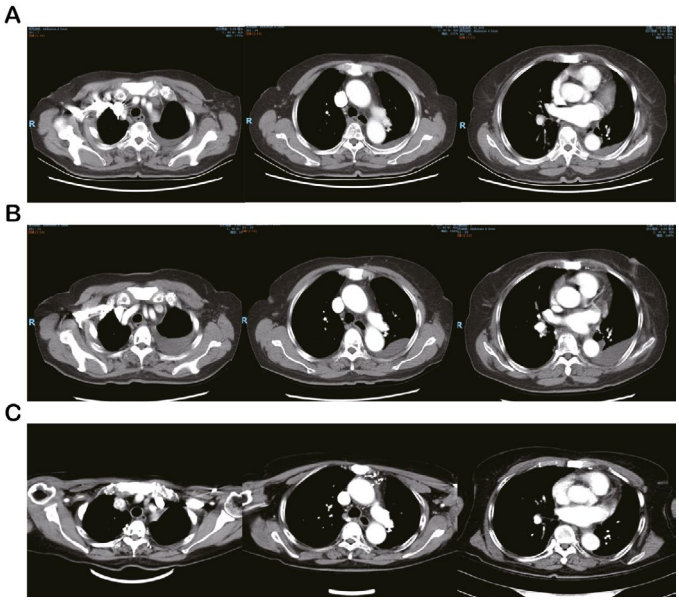

Figure 2 **Serial CT imaging illustrating the evolution of mediastinal lymphadenopathy and pleural effusion.**

(**A**) Chest CT on December 29, 2023, after two months of osimertinib treatment, shows a reduction in mediastinal lymph node size. (**B**) On March 1, 2024, malignant pleural effusion was identified, prompting initiation of bevacizumab combined with chemotherapy. (**C**) On December 16, 2024, follow-up CT revealed improved mediastinal lymphadenopathy and reduced pleural effusion after treatment.

In January 2025, the patient developed new neurological symptoms, including dizziness and headache. Cranial magnetic resonance imaging (MRI) was unremarkable, but cerebrospinal fluid cytology revealed malignant adenocarcinoma cells consistent with leptomeningeal metastasis (Fig. 3). She was therefore started on high-dose furmonertinib (240 mg daily) in combination with bevacizumab, resulting in progressive relief of neurological symptoms.

In May 2025, she experienced recurrent severe headache and vomiting, and a cerebrospinal fluid diversion procedure was performed to relieve intracranial hypertension (Fig. 3). Despite initial improvement, she developed persistent high fever and delirium in July 2025 and eventually died of presumed intracranial infection.

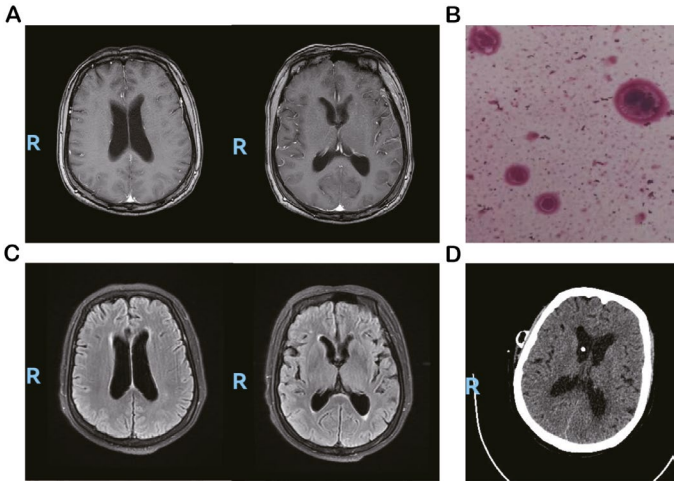

Figure 3 **Neuroimaging and cerebrospinal fluid findings associated with leptomeningeal metastases.**

(**A**) Brain MRI on January 1, 2025, revealed no significant abnormalities. (**B**) Cerebrospinal fluid cytology showed large atypical cells with abundant cytoplasm and eccentrically located, hyperchromatic nuclei. (**C**) After initiating furmonertinib 240 mg daily, the patient's dizziness improved; follow-up MRI on April 14, 2025, remained unremarkable. (**D**) On May 19, 2025, cerebrospinal fluid diversion was performed to relieve intracranial hypertension; high-density shadow in the ventricle represents the drainage catheter.

A chronological overview of the disease trajectory, treatment interventions, and outcomes is summarized in Fig. 4, highlighting the sequential application of surgery, targeted therapies, chemotherapy, radiotherapy, and neurosurgical procedures, as well as the dynamic adaptation of strategies in response to evolving disease progression.

DISCUSSION

Leptomeningeal metastases (LM) are a devastating complication of non-small cell lung cancer (NSCLC), often resulting in severe neurological symptoms, limited therapeutic options, and shortened survival.[7] Patients with *EGFR*-mutant NSCLC are particularly vulnerable, with an incidence of LM approaching 9%, compared to 3%–5% in the general NSCLC population.[8] Historically, prognosis has been poor, with a median overall survival (OS) of only 3–11 months despite intrathecal chemotherapy, whole-brain radiotherapy, or systemic chemotherapy.[9] The development of third-generation EGFR tyrosine kinase inhibitors (TKIs), which can penetrate the blood–brain barrier, has significantly improved central nervous system (CNS) outcomes, yet LM continues to represent a major clinical challenge.[10]

Furmonertinib is a novel, third-generation EGFR-TKI designed to achieve higher CNS drug exposure. Preclinical studies have demonstrated that its concentrations in brain tissue substantially exceed those in plasma.[11] Clinical evidence has confirmed these findings. In the pivotal phase III FURLONG trial, furmonertinib showed superior CNS progression-free survival (20.8 *vs* 9.8 months) and higher CNS response rates compared with gefitinib.[11] Real-world studies have further supported its CNS activity, particularly at higher doses. In one prospective study of 48 patients with LM, high-dose furmonertinib (240 mg daily) achieved a CNS disease control rate of 92% and a median OS of 8.4 months.[6] Several case reports also support dose escalation after osimertinib failure, with rapid neurological improvement and survival benefits.[12,13] These findings highlight the potential of furmonertinib as a salvage therapy for LM.

The present case provides several important insights. First, our patient achieved an OS exceeding six years from initial diagnosis,

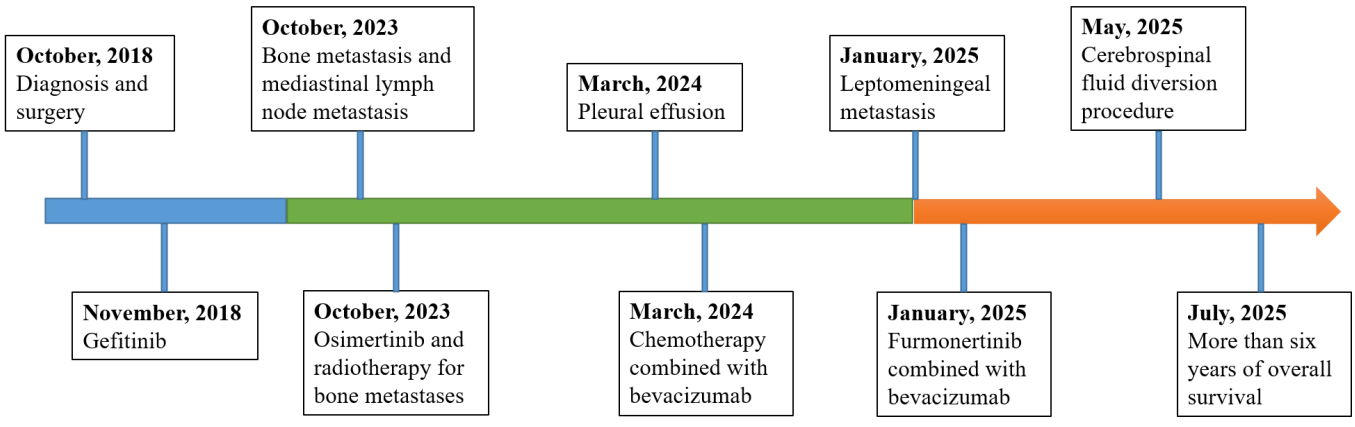

Figure 4 **Chronological timeline of the patient's clinical course, treatment interventions, and key clinical events.**

far longer than typically reported in stage IIB *EGFR*-mutant NSCLC with LM. This outcome underscores the value of sequential, individualized treatment strategies incorporating surgery, adjuvant EGFR-TKI, systemic chemotherapy, anti-angiogenic therapy, radiotherapy, and finally high-dose furmonertinib. Second, after failure of osimertinib and multiple systemic therapies, the initiation of furmonertinib 240 mg daily combined with bevacizumab provided meaningful neurological improvement and extended survival. This clinical benefit aligns with emerging evidence suggesting that high-dose furmonertinib can achieve therapeutic CNS concentrations and overcome some mechanisms of resistance. Third, the case illustrates the potential utility of combining furmonertinib with anti-angiogenic therapy, which may further enhance CNS disease control, as suggested in recent retrospective analyses.[14,15]

This report highlights a rare clinical course of *EGFR L858R*-mutant NSCLC with late-onset LM after multiple lines of therapy. Four key insights emerge: (i) LM remains a critical challenge in *EGFR*-mutant NSCLC, often arising despite prior TKI treatment; (ii) high-dose furmonertinib (240 mg daily), particularly when combined with anti-angiogenic agents, may provide neurological symptom control and survival benefit even after osimertinib failure; (iii) comprehensive and individualized treatment sequencing across modalities is essential for long-term disease control; and (iv) dose escalation strategies and multidisciplinary care should be considered in the evolving paradigm of CNS-directed therapy. Further prospective studies are needed to establish the optimal role of high-dose furmonertinib in this difficult-to-treat population.

Ethical Disclosures:

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