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High-Dose Osimertinib Combined with Intrathecal Pemetrexed for Leptomeningeal Metastases in EGFR-Mutant Non–Small Cell Lung Cancer: A Case Report and Literature Review

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Abstract **Case Report**

Leptomeningeal metastases represent one of the most severe complications of epidermal growth factor receptor (EGFR)–mutant non–small cell lung cancer (NSCLC) and are associated with substantial neurological morbidity and poor prognosis. Although osimertinib, a third-generation EGFR tyrosine kinase inhibitor, demonstrates superior central nervous system penetration compared with earlier-generation agents, isolated leptomeningeal progression may still occur due to pharmacokinetic sanctuary within the cerebrospinal fluid. We report the case of a 66-year-old man with metastatic EGFR-mutant lung adenocarcinoma who achieved durable systemic disease control with standard-dose osimertinib for 23 months before developing isolated leptomeningeal metastases confirmed by cerebrospinal fluid cytology. Given the stability of extracranial disease, therapeutic intensification with high-dose osimertinib at 160 mg daily combined with intrathecal pemetrexed was initiated, resulting in rapid neurological improvement and meaningful clinical stabilization. Neurological control was maintained for several months, and the patient survived nine months following treatment escalation. This report highlights the potential role of individualized central nervous system–directed strategies in selected patients with EGFR-mutant NSCLC and leptomeningeal progression.

Keywords: EGFR-mutant non–small cell lung cancer, leptomeningeal metastases, osimertinib, high-dose osimertinib, central nervous system metastases, intrathecal pemetrexed, targeted therapy.

INTRODUCTION

Leptomeningeal metastases occur in approximately 5–10% of patients with EGFR-mutant non–small cell lung cancer and represent one of the most aggressive patterns of metastatic dissemination, historically associated with rapid neurological deterioration and poor survival outcomes [1–3]. Despite major advances in molecularly targeted therapies, the leptomeningeal compartment remains a frequent site of therapeutic failure due to limited drug penetration and complex tumor–microenvironment interactions [4]. Osimertinib has become the standard first-line treatment for advanced EGFR-mutant NSCLC and has demonstrated superior systemic and central nervous system activity compared with earlier-generation EGFR tyrosine kinase inhibitors [5]. Nevertheless, isolated leptomeningeal progression may occur despite prolonged extracranial disease control, underscoring the need for optimized CNS-directed therapeutic strategies [6].

CASE PRESENTATION

A 66-year-old man with a medical history of controlled hypertension and a former smoking history of 40 pack-years, having ceased smoking ten years earlier, was diagnosed with metastatic lung adenocarcinoma harboring an activating EGFR mutation. Initial staging revealed diffuse bone metastases involving the axial skeleton, right adrenal metastasis, and peritoneal involvement.

First-line treatment with osimertinib at a dose of 80 mg daily was initiated in October 2023 in association with denosumab. The patient achieved a rapid and sustained systemic response, with radiological assessments confirming stable extracranial disease. The duration of response under standard-dose osimertinib was estimated at 23 months.

In October 2024, the patient presented with progressive headaches associated with intractable

vomiting. Brain imaging did not reveal parenchymal metastases or definitive leptomeningeal enhancement. Cerebrospinal fluid analysis demonstrated elevated protein levels, reduced glucose concentration, and the presence of malignant epithelial cells consistent with leptomeningeal carcinomatosis. Thoraco-abdomino-pelvic imaging confirmed persistent systemic disease stability.

Following multidisciplinary discussion, and given the isolated leptomeningeal progression with preserved extracranial disease control, osimertinib was escalated to 160 mg daily and intrathecal pemetrexed was initiated [8]. This therapeutic intensification resulted in rapid neurological improvement, with resolution of vomiting and marked reduction in headache intensity. Neurological stabilization was maintained for several months. The patient ultimately died nine months after treatment escalation.

Mechanistic Rationale for High-Dose Osimertinib

Osimertinib exerts its antitumor activity through irreversible inhibition of activating EGFR mutations and the T790M resistance mutation via covalent binding to the EGFR kinase domain [9]. Compared with first- and second-generation EGFR inhibitors, osimertinib demonstrates enhanced blood–brain barrier penetration; however, cerebrospinal fluid concentrations achieved at the standard dose of 80 mg daily remain substantially lower than plasma levels and may fall below the threshold required for sustained leptomeningeal disease control [10,11].

Dose escalation to 160 mg daily results in a proportional increase in systemic exposure and, critically, in cerebrospinal fluid concentrations [12]. Pharmacokinetic analyses have demonstrated a clear dose–exposure relationship, supporting the hypothesis that higher dosing may overcome subtherapeutic drug levels within the leptomeningeal compartment. Importantly, this strategy represents an optimization of target engagement rather than a changé in therapeutic mechanism, leveraging the favorable safety profile and therapeutic window of osimertinib.

The proposed pharmacokinetic and biological mechanisms underlying leptomeningeal progression and the rationale for osimertinib dose escalation are illustrated in Figure1.

Review of the Literature and Evidence Synthesis

Clinical evidence supporting high-dose osimertinib and intrathecal chemotherapy in leptomeningeal metastases is summarized in **Table 1** [12–16,18,19]. The phase I BLOOM study provided the first prospective demonstration of meaningful neurological improvement and prolonged survival with osimertinib 160 mg daily in patients with leptomeningeal metastases [12]. Subsequent real-world cohorts and retrospective series have confirmed these findings, reporting symptom improvement, cytological responses, and survival outcomes exceeding historical benchmarks [13–16].

DISCUSSION

The present case highlights several critical aspects of leptomeningeal metastases management in EGFR-mutant NSCLC. First, the prolonged systemic disease control achieved with standard-dose osimertinib underscores the sustained efficacy of third-generation EGFR inhibition at the extracranial level. Second, the emergence of isolated leptomeningeal progression reinforces the concept of the leptomeningeal space as a pharmacokinetic sanctuary, where drug exposure remains suboptimal despite adequate systemic concentrations [4,10].

The decision to escalate osimertinib rather than switch systemic therapy reflects a paradigm shift increasingly supported by pharmacokinetic data and clinical evidence. Dose escalation enables enhanced cerebrospinal fluid penetration and improved target inhibition within the leptomeningeal compartment, without abandoning an otherwise effective systemic therapy [12–16]. This strategy is particularly relevant in patients with preserved performance status, stable extracranial disease, and absence of alternative resistance mechanisms.

The integration of intrathecal pemetrexed further exemplifies a rational multimodal approach aimed at overcoming anatomical and pharmacological barriers. By delivering cytotoxic therapy directly into the cerebrospinal fluid, intrathecal pemetrexed may synergize with systemic EGFR inhibition and contribute to rapid symptom control and neurological stabilization [18,19].

Beyond survival outcomes, neurological symptom control and quality-of-life preservation represent clinically meaningful endpoints in this setting. The nine-month survival observed following treatment intensification in this patient compares favorably with historical data and aligns with outcomes reported in contemporary series.

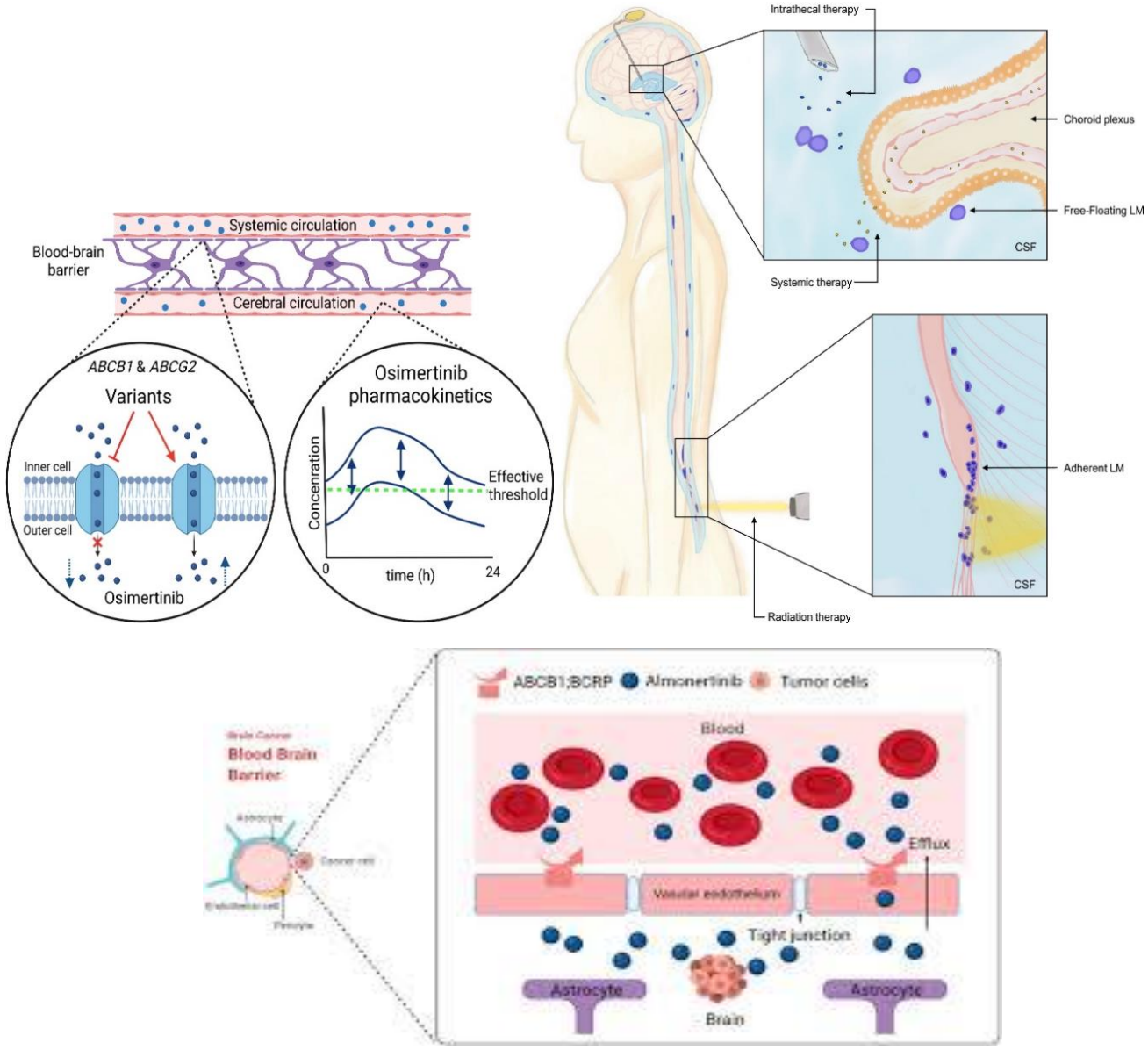

Figure 1: ***Mechanistic rationale for osimertinib dose escalation.*** **Standard-dose osimertinib achieves effective systemic and parenchymal CNS control but may result in insufficient cerebrospinal fluid exposure. Dose escalation increases CSF drug concentration, enhancing EGFR inhibition within the leptomeningeal compartment. Intrathecal pemetrexed provides complementary direct cytotoxic exposure within the CSF**

Table 1: Published studies evaluating high-dose osimertinib and intrathecal therapy in leptomeningeal metastases

Study	Design	Patients (n)	Intervention	Key Outcomes	Ref.
Yang et al.	Phase I (BLOOM)	41	Osimertinib 160 mg	Median OS 11 months	[12]
Reungwetwattana *et al.,*	Subgroup analysis	128	Osimertinib 80 mg	Superior CNS control	[13]
Nanjo *et al.,*	Case series	5	Osimertinib 160 mg	Neurological improvement	[14]
Saboundji *et al.,*	Real-world cohort	14	Osimertinib 80–160 mg	Median OS 8–12 months	[15]
Piper-Vallillo *et al.,*	Multicenter retrospective	105	Dose escalation	CNS disease stabilization	[16]
Pan *et al.,*	Prospective study	34	Intrathecal pemetrexed	Clinical and cytological response	[18]
Fan *et al.,*	Case series	13	Intrathecal pemetrexed	Symptom control	[19]

Additional Considerations and Future Directions

Emerging data suggest that cerebrospinal fluid molecular profiling, dynamic monitoring of drug concentrations, and early identification of leptomeningeal involvement may further refine patient selection and treatment timing. Prospective studies integrating pharmacokinetic biomarkers and patient-reported outcomes are warranted to optimize therapeutic strategies and establish standardized algorithms for leptomeningeal disease management.

Limitations

This report describes a single patient experience and is therefore subject to the inherent limitations of case-based evidence. Cerebrospinal fluid drug concentrations and serial molecular analyses were not available, limiting pharmacodynamic correlation. Nevertheless, the clinical course observed is consistent with pharmacokinetic data and convergent evidence from prospective and real-world studies

CONCLUSION

This case supports the role of high-dose osimertinib combined with intrathecal chemotherapy as a rational, mechanism-based strategy in selected patients with EGFR-mutant NSCLC and isolated leptomeningeal progression. Optimizing central nervous system drug exposure while maintaining effective systemic therapy represents a clinically meaningful approach that aligns with emerging evidence and expert recommendations.

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