Oncology Advances **2023** vol. 1(1) | 35–38
DOI: 10.14218/OnA.2023.00011

Case Report

Neurological Involvement in EGFR-mutated Non-small-cell Lung Cancer: A Case Report of Third-generation EGFR-tyrosine Kinase Inhibitor Response

Anna Ianza[1*], Angela Dicorato[1], Furlanis Giovanni[2], Francesca Currò[3], Valentina Orlando[1] and Alessandra Guglielmi[1]

[1]*Oncology Department, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Italy;* [2]*Clinical Unit of Neurology, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Italy;* [3]*Radiology Department, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Italy*

Received: June 05, 2023 | **Revised:** July 31, 2023 | **Accepted:** October 31, 2023 | **Published online:** December 5, 2023

Abstract

Patients with non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations benefit from targeted therapy with tyrosine kinase inhibitors (TKIs). Nevertheless, 50–70% of patients will experience progressive disease during TKI therapy, and nearly half will develop resistance mutations such as T790M, for which a third-generation TKI has been developed and proven to be highly effective. One of the most common sites of metastasis in patients with NSCLC is the central nervous system, significantly impacting their and their relatives' quality of life as well as the management of the disease. A patient diagnosed with stage IV lung adenocarcinoma showed progression after 21 months of first-line anti-EGFR therapy and showed clear signs of neurological impairment. The interpretation of cerebral involvement was dubious and difficult: while cerebral spinal fluid cytology seemed to confirm leptomeningeal carcinomatosis, no meningeal nodules or abnormal enhancement was detected on magnetic resonance imaging. Liquid biopsy detected the resistance mutation T790M; hence, therapy was switched to the third-generation TKI osimertinib. The first instrumental re-evaluation revealed a partial response, with a reduction in both lung lesion dimensions and brain alterations. This case shows the effectiveness of osimertinib in treating patients with stage IV NSCLC with central nervous system and bone involvement.

Introduction

Lung cancer is the second most common cancer in men and women and the leading cause of cancer-related deaths worldwide. Most lung cancers (85%) are classified as non-small cell lung cancer (NSCLC), and most patients with NSCLC are already at an advanced stage when diagnosed.[1,2] In advanced stages, the therapeutic strategy is often driven by the mutational status of the malignancy.

Keywords: NSCLC; TKI; Osimertinib; Central nervous system involvement; Target therapy.

Abbreviations: CT, computed tomography; EGFR, epidermal growth factor receptor; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; SUV, standardized uptake value; TKI, tyrosine kinase inhibitor.

[*]**Correspondence to:** Anna Ianza, Oncology Department, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste 34129, Italy. ORCID: https://orcid.org/0000-0002-3527-8040. Tel: +39-040-3992-375, Fax: +39-040-3992-490, E-mail: anna.ianza@asugi.sanita.fvg.it

How to cite this article: Ianza A, Dicorato A, Giovanni F, Currò F, Orlando V, Guglielmi A. Neurological Involvement in EGFR-mutated Non-small-cell Lung Cancer: A Case Report of Third-generation EGFR-tyrosine Kinase Inhibitor Response. *Oncol Adv* 2023;1(1):35–38. doi: 10.14218/OnA.2023.00011.

Mutations in the epidermal growth factor receptor (EGFR) gene have led to the development of the EGFR-targeted therapy that revolutionized NSCLC management in the last two decades. The first, second, and third generations of oral EGFR tyrosine kinase inhibitors (TKIs) have shown superiority over standard platinum-based chemotherapy in at least 8 randomized phase III studies, both in terms of response rate and progression-free survival.[3–6] Moreover, new TKIs are being considered as the first-line option in patients with EGFR mutations, alongside new strategies to overcome the frequently occurring acquired resistance. Despite response rates between 50% and 70%, disease progression occurs on average after 9 to 13 months of EGFR-TKI treatment.[7] T790M is a resistance mutation found in nearly 50% of patients who progress under first-line TKI treatment.[8] Osimertinib (Tagrisso) is a third-generation EGFR-TKI that specifically targets the T790M mutated cells, and it was approved by the European Medicines Agency in January 2019 for first- or second-line treatment. Its superiority over platinum-based treatment in terms of progression-free survival, overall response rate, and duration of response has been demonstrated in the AURA 3 trial.[9]

From a clinical point of view, we can identify at least three dis-

tinct patterns of progression: isolated central nervous system progression, oligoprogression, and widespread systemic progression. Brain metastases are common in those affected by NSCLC, with nearly 40% of patients developing them.[10] This progression often deeply affects the survival rate, therapy response, compliance, and quality of life. On average, patients with untreated brain metastasis survive 6 months to 1 year from diagnosis.[11] Common treatments include whole-brain or stereotactic radiotherapy, although frequent adverse events like cognitive problems and memory loss significantly deter treatment.[12]

Leptomeningeal carcinomatosis is a devastating result of late-stage cancer and remains rapidly fatal despite multimodal treatment. Definitive diagnosis requires the identification of malignant cells in the cerebrospinal fluid or obvious disease on magnetic resonance imaging (MRI).[13] Leptomeningeal carcinomatosis occurs in 5–15% of patients with cancer; treatment options are limited, and median survival time ranges from 2 to 6 months.[14]

More recently, as next-generation targeted therapy and immunotherapy became routine in clinical practice, clinicians are questioning the capability of new drugs to cross the blood-brain barrier and eventually influence the course of the illness and the management of brain metastasis.

This manuscript was prepared according to the CARE guidelines, and the associated checklist was completed.

Case presentation

A 70-year-old non-smoking woman was diagnosed with lung adenocarcinoma in March 2019. Whole-body computed tomography (CT) showed a solid lesion in the right upper lobe of the lung, with a maximum diameter of about 5 × 5 cm. The scan also showed micronodularity and increased density of the surrounding tissue, a ground-glass area at the middle lobe, and a 5-mm nodule at the anterior segment of the right upper lobe. In the left lung, there were some micronodularities, particularly in the anterior upper lobe. Small, enlarged pretracheal lymph nodes with a maximum diameter of approximately 14 mm were noted. Multiple larger lymph nodes were present in the right hilar site forming a body with the mass, and others were in the subcarinal region. Baseline total body CT did not show any brain or skeletal lesions; surgical removal was ruled out owing to the presence of skeletal metastases on positron emission tomography/CT images that revealed uptakes in the left anterior extremity of the third rib with a standardized uptake value (SUV) of 4.2, sectors posterior to the iliac sacrum (SUV 3.8), and the right ischium (SUV 5), confirming the metastatic stage.

The mutational status of the EGFR gene was determined on a histological specimen from a biopsy (fiberoptic bronchoscopy) of an endobronchial lesion, which revealed an EGFR mutation in exon 19 (deletion). The molecular biology investigation was conducted using real-time PCR after extraction with Mag Core genomic DNA FFPE One Step Kit. Afatinib 30 mg was administered to the patient from April 2019 to February 2021. The dose was reduced to 20 mg in August 2019 owing to dermatologic toxicity (mucositis) grade 2–3. The best response to targeted therapy was a partial response (CT of July 2019) followed by stable disease in subsequent CT evaluations. After 6 months of therapy, oligoprogression was observed in the sacral bone. Consequently, the patient received 5 fractions of 20 Gy radiation for palliative purposes. In August 2020, the patient showed apathy, asthenia, and mood deflection, initially diagnosed and treated as depression. Progressively, the patient and her caregiver reported a loss of balance and lack of coordination in walking, causing frequent falls. The patient's relatives reported that she showed a worsening in cognitive functions and difficulties in carrying out daily tasks, such as using household appliances and remote controls, among others.

This study was performed following the ethical standards of the affiliated institutions and in compliance with the Declaration of Helsinki (revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Investigations

Brain CT performed in November 2020 did not reveal any lesions. Neurological examination highlighted gait ataxia, cerebellar dysmetria in upper and lower limbs, ideomotor slowdown, and cognitive impairments, as evidenced by a Montreal Cognitive Assessment score of 7 out of 30. Brain MRI conducted in December 2020 showed cortical atrophy and multiple asymmetrical bilateral FLAIR hyperintensities involving the frontoparietal cortex, basal ganglia, mesencephalus, and right cerebellar hemisphere. The lesions did not show enhancements after gadolinium administration, and only the lesion located in the mesencephalus showed restriction on diffusion-weighted imaging.

Electroencephalogram showed slowing of background activity, with a predominant theta rhythm (Fig. 1). In January 2021, positron emission tomography/CT of the brain showed signs of reduced metabolism in the dorsolateral and mesial frontal lobes, superior parietal lobes, and caudate nuclei, while showing increased metabolism in the cerebellar vermis and cerebellar tonsils. Brain MRI interpretation was very ambiguous. The FLAIR hyperintensity involving the cortex, basal ganglia, and brainstem did not show the typical characteristics of brain metastases or meningeal carcinomatosis; hence, paraneoplastic syndrome/encephalitis was suspected.[15]

The patient underwent rachicentesis for cerebral fluid analysis. Cerebral fluid cytology showed the presence of carcinomatous cells. Whole-body positron emission tomography/CT revealed pulmonary and skeletal progression of the primitive lung disease.

Treatment

Due to the clinical and instrumental evidence of disease progression along with the detection of resistance mutation T790M, therapy with afatinib was stopped. The resistance mutation was detected on plasma via liquid biopsy by real-time PCR using the EasyPGX® ready EGFR kit (Diatech Pharmacogenetics, Ancona, Italy). In February 2021, the patient started therapy with osimertinib 80 mg per day, which was ongoing at the time of writing. Owing to a depressive state characterized by apathy, selective serotonin reuptake inhibitor therapy was introduced, showing clinical benefits.

Discussion

The patient underwent periodic neurological checks and instrumental follow-ups (abdomen-thorax CT and brain MRI) every 3 months as part of osimertinib therapy. The first instrumental re-evaluation in April 2021 highlighted a partial response in both CT and brain MRI. CT of the thorax showed a decrease in the size of the right pulmonary hilar lesion, and brain MRI showed diffuse reduction of FLAIR hyperintensity in the cerebral cortex, basal ganglia, mesencephalus, and right cerebellar hemisphere (Fig. 1).

At the latest re-evaluation in February 2022, after 12 months of second-line targeted therapy, CT and brain MRI showed stable disease. A follow-up electroencephalogram showed an improve-

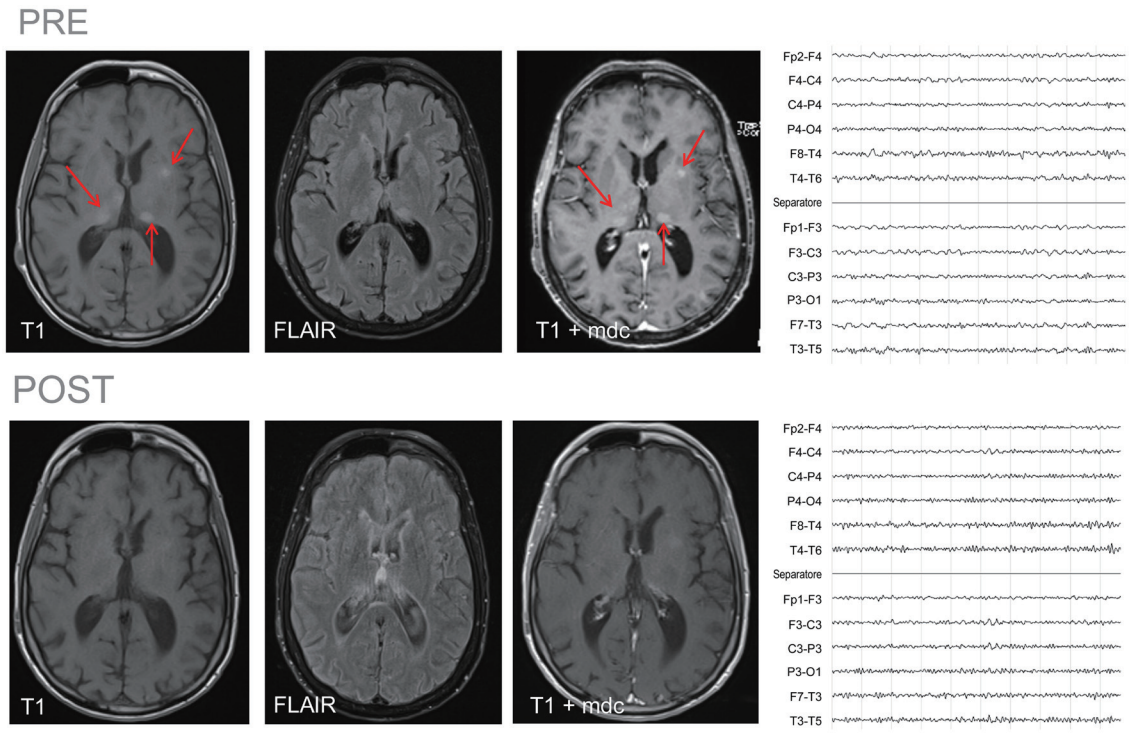

Fig. 1. Brain magnetic resonance images with and without contrast medium (mdc) before (PRE; December 2020, upper photo) and after osimertinib therapy (POST; February 2022, lower photo), and electroencephalogram readings before (PRE; December 2020, upper photo) and after osimertinib therapy (POST; March 2022, lower photo). FLAIR, fluid attenuated inversion recovery.

ment in background activity, with a greater representation of alpha rhythms and a reduction in theta and delta components. Neurological examination showed stability (Fig. 1).

Conclusions

Osimertinib, a third-generation TKI, in addition to its well-documented efficacy in the treatment of EGFR-mutated lung lesions compared to platinum therapy alone,[9] demonstrates efficacy in monitoring the clinical evolution of nervous system involvement, a common feature in these patients. Notably, the neurological symptoms of the patient in this case considerably subsided within the first few months of therapy. The authors hope that the rapid and detrimental evolution of the disease, especially in cases with central nervous system involvement, can be slowed down, given the observed significant reduction in brain lesions.

Collaboration and support from family or home caregivers are essential to ensure optimal care of cancer patients with cognitive impairment. Equally important is the continuous and transparent collaboration between specialists, in particular oncologists and neurologists, which can ensure a full understanding of disease evolution and foster the development of an appropriate therapeutic strategy.

Recent studies suggest that osimertinib has a higher permeability in the central nervous system compared to other TKIs, regardless of whether the patients harbor the T790M mutation.[16] A thorough discussion is needed to determine the most appropriate and effective time to start the therapy, emphasizing the importance of early detection of resistance mutations to EGFR-targeted therapy. Comparative studies between first-, second-, and third-generation target therapies (EGFR and ALK targeted) in this area of study may shed light on the impact of brain metastasis control on the clinical management of lung cancer.

Acknowledgments

A previous preliminary version of these data was previously published as an abstract in the Chest Congress 2022. Since then, the data have been updated and the diagnosis has been revised. The authors would like to thank Matteo di Franza for his editorial assistance and English proofreading.

Funding

None.

Conflict of interest

The authors declare that they have no conflict of interests related to the publication.

Author contributions

Study concept and design (AG, AI, and AD), oncological insight, data analysis, and interpretation (VO, AD), radiological insights, data analysis, and interpretation (FC), and neurological assessments, analysis, and interpretation of data for the work (GF). All authors drafted the work and revised it critically for important intellectual content. All authors read and approved this final version to be published.

Ethics statement

This study was performed following the ethical standards of the institutions to which we are affiliated and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Data sharing statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author at anna.ianza@asugi.sanita.fvg.it upon reasonable request.

References

[1] Ianza A, Dicorato A, Guglielmi A, Orlando V, Furlanis G, Currò F. Neurological Evolution Of A Patient With EGFR Mutated Non-Small Cell Lung Cancer. Chest congress 2022;161(6):A333. doi:10.1016/j.chest.2021.12.363.

[2] Testa U, Castelli G, Pelosi E. Lung Cancers: Molecular Characterization, Clonal Heterogeneity and Evolution, and Cancer Stem Cells. Cancers (Basel) 2018;10(8):248. doi:10.3390/cancers10080248, PMID:30060526.

[3] Wang S, Cang S, Liu D. Third-generation inhibitors targeting EGFR T790M mutation in advanced non-small cell lung cancer. J Hematol Oncol 2016;9:34. doi:10.1186/s13045-016-0268-z, PMID:27071706.

[4] Kim HR, Lee SY, Hyun DS, Lee MK, Lee HK, Choi CM, *et al*. Detection of EGFR mutations in circulating free DNA by PNA-mediated PCR clamping. J Exp Clin Cancer Res 2013;32(1):50. doi:10.1186/1756-9966-32-50, PMID:23927790.

[5] Punnoose EA, Atwal S, Liu W, Raja R, Fine BM, Hughes BG, *et al*. Evaluation of circulating tumor cells and circulating tumor DNA in non-small cell lung cancer: association with clinical endpoints in a phase II clinical trial of pertuzumab and erlotinib. Clin Cancer Res 2012;18(8):2391–2401. doi:10.1158/1078-0432.CCR-11-3148, PMID:22492982.

[6] He C, Liu M, Zhou C, Zhang J, Ouyang M, Zhong N, *et al*. Detection of epidermal growth factor receptor mutations in plasma by mutant-enriched PCR assay for prediction of the response to gefitinib in patients with non-small-cell lung cancer. Int J Cancer 2009;125(10):2393–2399. doi:10.1002/ijc.24653, PMID:19530244.

[7] Rossi A, Galetta D. Systemic Therapy for Oligoprogression in Patients with Metastatic NSCLC Harboring Activating EGFR Mutations. Cancers (Basel) 2022;14(3):832. doi:10.3390/cancers14030832, PMID:35159099.

[8] Kobayashi S, Boggon TJ, Dayaram T, Jänne PA, Kocher O, Meyerson M, *et al*. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med 2005;352(8):786–792. doi:10.1056/NEJMoa044238, PMID:15728811.

[9] Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, *et al*. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med 2017;376(7):629–640. doi:10.1056/NEJMoa1612674, PMID:27959700.

[10] Gandara DR, Li T, Lara PN, Kelly K, Riess JW, Redman MW, *et al*. Acquired resistance to targeted therapies against oncogene-driven non-small-cell lung cancer: approach to subtyping progressive disease and clinical implications. Clin Lung Cancer 2014;15(1):1–6. doi:10.1016/j.cllc.2013.10.001, PMID:24176733.

[11] Healey N. Better treatments for lung cancer that spreads to the brain. Nature 2020;587(7834):S14–S15. doi:10.1038/d41586-020-03155-x, PMID:33208971.

[12] Hartgerink D, van der Heijden B, De Ruysscher D, Postma A, Ackermans L, Hoeben A, *et al*. Stereotactic Radiosurgery in the Management of Patients With Brain Metastases of Non-Small Cell Lung Cancer: Indications, Decision Tools and Future Directions. Front Oncol 2018;8:154. doi:10.3389/fonc.2018.00154, PMID:29868476.

[13] Bhambhvani HP, Rodrigues AJ, Umeh-Garcia MC, Hayden Gephart M. Leptomeningeal Carcinomatosis: Molecular Landscape, Current Management, and Emerging Therapies. Neurosurg Clin N Am 2020;31(4):613–625. doi:10.1016/j.nec.2020.06.010, PMID:32921356.

[14] Nayar G, Ejikeme T, Chongsathidkiet P, Elsamadicy AA, Blackwell KL, Clarke JM, *et al*. Leptomeningeal disease: current diagnostic and therapeutic strategies. Oncotarget 2017;8(42):73312–73328. doi:10.18632/oncotarget.20272, PMID:29069871.

[15] Liu C, Zhang Y, Li Y, Bu H, Meng Z, Ji Y, *et al*. A rare magnetic resonance imaging pattern of leptomeningeal carcinomatosis: a case description. Quant Imaging Med Surg 2021;11(7):3367–3370. doi:10.21037/qims-20-45, PMID:34249661.

[16] Li D, Song Z, Dong B, Song W, Cheng C, Zhang Y, *et al*. Advances in targeted therapy in non-small cell lung cancer with actionable mutations and leptomeningeal metastasis. J Clin Pharm Ther 2022;47(1):24–32. doi:10.1111/jcpt.13489, PMID:34309914.