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# Complete response in a lung adenocarcinoma with pleural metastases initially treated with gefitinib and switched to osimertinib after cerebral oligo-progression with unknown T790M mutation: a case report and review of literature

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## Abstract

**Background** First- and second-generation anti-epithelial growth factor receptor tyrosine kinase inhibitors have shown great efficacy in the treatment of advanced adenocarcinoma with epithelial growth factor receptor mutations, but this efficacy is limited by certain resistance mechanisms, in particular the T790M mutation, which must be screened before second-line treatment with osimertinib is indicated. The search for this mutation is sometimes difficult, especially in cases of intracranial relapse, through this case report we attempt to discuss the possibility of initiating treatment with osimertinib despite an unknown T790M mutation in such situation.

**Case report** We present the case of a 70-year-old Moroccan male patient diagnosed with non-small cell lung carcinoma initially metastatic to the pleura with an epithelial growth factor receptor mutation who received gefitinib in first line with a complete response, he subsequently presented with cerebral oligo-progression with extra cranial stability. The patient was started on osimertinib with unknown T790M status, as it was impossible to perform a cerebral biopsy, the evolution was characterized by a partial response followed by stereotactic radiotherapy then a complete response for 2 years.

**Conclusion** We can discuss osimertinib as an option for patients with stage IV non-small cell lung cancer with brain oligo-progression on prior tyrosine kinase inhibitors and unknown T790M status, further studies are needed in this area.

**Keywords** NSCLC, EGFR mutation, Gefitinib, T790M mutation, Osimertinib, Cerebral oligo-progression

## Introduction

Lung cancer is the leading cause of cancer death worldwide; the most common histological subtype is non-small cell lung cancer (NSCLC) [1, 2]. These cancers are diagnosed most often at an advanced stage [3, 4].

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Adenocarcinoma is the most common histological subtype of non-small cell lung carcinoma [2–6], in the case of advanced or metastatic disease, treatment necessarily requires the search for mutations involved in carcinogenesis, including the epithelial growth factor receptor (EGFR) mutation. The discovery of an oncogenic driver makes it possible to indicate targeted therapy for the patient [5].

EGFR mutation is the most common in NSCLC and its frequency varies according to ethnicity, affecting around 10% of the Caucasian population and up to 50% of the Asian population [5]; in the Moroccan population, the frequency of EGFR mutation is estimated at 21.9% [7].

Patients with mutated EGFR are more likely to develop brain metastases [8–11], overall survival is better in patients with EGFR + stage IV NSCLC; however brain metastases are considered to be a poor prognostic survival factor [9].

Treatment with an anti EGFR tyrosine kinase inhibitor is the standard first line treatment for advanced NSCLC with EGFR mutations. First generation tyrosine kinase inhibitors (TKIs) (erlotinib and gefitinib) and second generation TKIs (Afatanib) have been shown to be very effective and have been validated by clinical trials [12–14], at progression, two-thirds of these patients have a resistance mutation represented by the T790M mutation, which is the most frequent resistance mechanism [16], this mutation reduces the affinity of first and second generation TKIs for EGFR adenosine triphosphate (ATP), which hinders the blocking of tumor signal transduction and leads to disease progression [15–18].

Osimertinib is a third generation irreversible TKI with improved penetrance in the central nervous system, targeting sensitive EGFR mutations as well as those with the T790M resistance mutation [19, 20].

Osimertinib has been validated as a first-line treatment for patients with EGFR positive stage IV NSCLC [21, 22] as well as for patients who have progressed on first- or second-generation TKIs with T790M mutation compared with platinum-pemetrexed-based chemotherapy, including patients with brain metastases, as demonstrated by the phase III AURA 3 study [15]. The progression-free survival (PFS) in the central nervous system (CNS) reached 11.7 months [23].

In this case report, we attempt to discuss the problematic situation of patients with stage IV EGFR-mutant adenocarcinoma who present with cerebral progression on first- and second-generation tyrosine kinase inhibitors. In these patients, re-biopsy to look for the T790M mutation and administration of osimertinib is often very difficult, especially if a complete response is achieved extracranially. Despite the efficacy of osimertinib in the brain, there is a lack of evidence in literature for these patients, which could lead to undertreatment and loss of opportunity and benefit for some of them.

## The case

A 70-year-old man, of Moroccan nationality, lawyer by profession, former smoker with 1.5 packs a year, without comorbidities or pathological history, presented 7 years ago with left basithoracic pain; a computed tomography (CT) scan of the chest was requested, showing the presence of a left pleural thickening.

A thoracoscopy was performed showing pleural involvement in the form of disseminated nodules, a pleural biopsy was performed and the pathological examination showed the presence of a TTF1 + adenocarcinoma.

A positron emission tomography (PET) scan was performed and showed a single pleural involvement with no other distant secondary sites.

Molecular biology revealed an EGFR mutation and the decision was made to treat the patient with an anti-EGFR tyrosine kinase inhibitor, Gefitinib at a dose of 250 mg per day. He achieved a partial response at the first assessment and then a near complete response that was maintained for 5 years.

The treatment was very well tolerated, with the exception of a grade 1 muco-cutaneous rash, which resolved rapidly.

After 5 years of treatment with gefitinib, the patient presented with dizziness, he only consulted a month later after a fall, the ear, nose, and throat (ENT) examination was normal. On PET scanner, we observed extensive hyper-metabolic brain lesions in the right temporal and left parietal regions.

We requested a cerebral magnetic resonance imaging (MRI) for better characterisation, which showed right temporal and left occipital processes compatible with metastatic lesions.

Biopsy of these lesions was discussed, but was considered technically difficult by neurosurgeons; the patient also refused any brain biopsy. The T790M mutation was therefore unknown; a liquid biopsy could have been done, but it was not reimbursed by his insurance.

A proposal to continue with gefitinib and treat locally with radiotherapy was discussed, but rejected as the lesions could not be included in a stereotactic radiotherapy field with a high risk of blindness.

Finally, it was decided to start treatment with a third-generation anti-EGFR tyrosine kinase inhibitor, osimertinib at 80 mg per day, because of its good blood–brain barrier diffusion.

After 3 months of treatment, the patient reported a clear clinical improvement; the requested brain MRI showed a partial response.

Therefore, stereotactic body radiation therapy (SBRT) was indicated after discussion regarding risk; the patient was irradiated on both lesions. Evaluation after SBRT and at 6 months by brain MRI showed a complete response.

The tolerability of osimertinib was excellent, at month 10 the patient presented with a large, very painful vesicular plaque on the back and wanted to stop treatment; on clinical examination we found that it was a shingles infection (Fig. 1), this event was treated with oral and topical acyclovir. Osimertinib was not stopped as there is no risk of interaction between the two molecules.

## Discussion

Our patient presented with a single cerebral relapse on gefitinib, with stable extra cranial lesions. Given the location of the tumor and the risks involved, we were unable to perform a biopsy of the cerebral lesions, and the liquid biopsy was difficult to access to search for the T790M resistance mutation. We were also unable to continue gefitinib and treat the cerebral lesions locally by surgery or SBRT, these techniques in addition to whole brain radiation therapy (WBRT) are frequently responsible for side effects and possible alteration of the general state, which may delay or cancel systemic treatment [24–26].

For patients with a single cerebral relapse who have progressed on first or second generation TKIs, searching for the T790M mutation to indicate treatment with osimertinib is often difficult, especially in the absence of a biopsiable extracranial site, as in the case of our patient. Testing for the mutation using circulating plasma *DNA* is an interesting option. However, this liquid biopsy is not always available; in addition, data concerning the sensitivity of mutation research are not solid, this would be attributed to the low availability of the mutation in plasma and tumor heterogeneity [24].

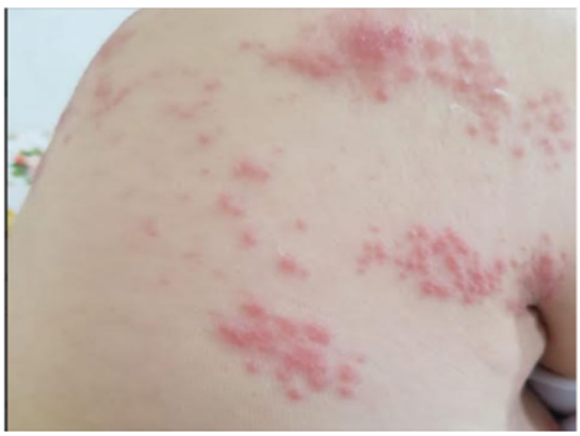

**Fig. 1** After 21 months of taking osimertinib, complete response was maintained in the brain and lungs; we decided to continue the treatment given the clinical response and good tolerability

Significant differences in T790M mutation status between biopsy of brain metastases and liquid biopsy have been reported in patients who have progressed on first and second generation TKIs [3]. Liquid biopsy is 30–60% less sensitive than tissue biopsy in detecting this mutation using polymerase chain reaction (PCR) or next generation sequencing (NGS) [27, 28]. This may mean that a large proportion of these patients are undertreated with osimertinib.

It is important to know that only half the patients resistant to first and second generation TKIs could benefit from tissue rebiopsy [29, 30].

We therefore decided to treat our patient with osimertinib despite the unknown T790M status. Osimertinib proved to be effective in our patient and the response achieved allowed subsequent consolidation with SBRT. The OCEAN study is a prospective phase II trial that demonstrated the efficacy of osimertinib in patients with radiotherapy naive NSCLC with central nervous system metastases in the two cohorts of the study: the T790M + cohort (previously treated) and the first-line cohort (untreated). These data are consistent with the results we obtained in our patient, especially if we assume that he is T790M positive [31, 32].

Osimertinib has already demonstrated its efficacy in intracranial involvement in EGFR-mutated patients pretreated with first or second generation TKIs, with a good safety profile [8–38]; as well as in EGFR TKI-naive patients in whom the phase III FLAURA study demonstrated a 50% reduction in the risk of intracranial progression with osimertinib compared with erlotinib and gefitinib, with a median response of 15. 2 months [34]. This efficacy was demonstrated regardless of the T790M mutation in patients with leptomeningeal disease [19–35].

A retrospective, real-life study evaluated osimertinib treatment in 25 patients with EGFR-mutated advanced non-small cell lung carcinoma who had already received a first- or second-generation TKI independently of the T790M mutation, with intracranial oligoprogression and extra cranial stability. Overall, 17 patients had started osimertinib after genotyping on circulating plasma *DNA*, of whom 8 patients had a positive T790M mutation and 9 had a negative T790M mutation. The remaining eight patients had started treatment with an unknown T790M mutation status; this study found no difference in PFS between the three groups and considered osimertinib to be an effective option in patients with isolated intracranial progression after first-generation anti EGFR TKI, regardless of plasma T790M status [24].

A retrospective study was carried out on patients who underwent rebiopsy after failure of a first line tyrosine kinase inhibitor. This study assessed the results in the T790M-positive and negative populations. The T790M mutation was considered to be a good clinical prognostic factor, however, this study showed that this mutation was much less present in cases of CNS involvement, with a percentage of 17% compared with 41% in extra-cranial involvement. This may be explained by the existence of resistance mechanisms other than the T790M mutation in the CNS, or by the low penetrance of first and second generation TKIs in the blood–brain barrier (BBB) [3]. This idea is supported by a number of studies that have demonstrated the efficacy of high-dose TKIs in cases of CNS involvement [36–38].

Our patient progressed on gefitinib only in the brain, with a complete response in the pleura. It should be noted that cerebral progression to first and second generation TKIs accounts for 40% of resistant patients [39]. Passage through the BBB may be considered the most influential factor on the efficacy of osimertinib compared with other TKIs. The APOLLO study showed BBB penetration of 31. 7% for osimertinib, clearly exceeding that of the other TKIS, all of which did not reach 6% [39–42]; this also explains the objective responses in patients with negative or unknown T790M [24–43]. Progression with first and second generation TKIs may be owing to bioavailability and not to resistance linked to the T790M mutation.

A review of literature and a meta-analysis were carried out to demonstrate the efficacy of osimertinib in patients already treated with TKIs with different T790M statuses, which showed that in patients with brain metastases in progression undergoing first or second generation TKIs, osimertinib demonstrated efficacy whatever the T790M mutation status (negative or unknown) and should be used in this situation [7], This also applies to patients with a negative T790M mutation on liquid biopsy and no genotyping on tumor tissue (given the risk of false negatives). In this meta-analysis and for the population of patients with brain metastases, there were no differences in overall survival (OS) between patients with T790M + and— mutations, and between the T790M + population and that with unknown status [7].

## Conclusion

Metastatic lung adenocarcinoma remains a therapeutic challenge. The discovery of a mutation in the EGFR receptor means that treatment is potentially effective with satisfactory tolerability; treatment with first- and second-generation anti-EGFR tyrosine kinase inhibitors is limited by the emergence of resistance mechanisms, in particular the T790M mutation. Searching for this mutation to administer treatment with osimertinib is not always possible, especially in cases of intracranial relapse, owing to the difficulty of obtaining a tissue biopsy and the high cost of molecular biology tests and therefore the lack of access for patients in developing countries. The data cited in our article support the use of osimertinib in our patient after cerebral oligoprogression on gefitinib with an unknown T790M mutation; however, more solid analyses and studies on this type of patient will be of great use in our practice.

### Abbreviations

| | |
|---|---|
| NSCLC | Non-small cell lung cancer |
| SBRT | Stereotactic body radiation therapy |
| WBRT | Whole brain radiation therapy |
| EGFR | Epithelial growth factor receptor |
| MRI | Magnetic resonance imaging |
| PET | Positron emission tomography |
| ENT | Ear, nose, and throat |
| TKI | Tyrosine kinase inhibitor |
| CNS | Central nervous system |
| CT | Computed tomography |
| BBB | Blood–brain barrier |

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### Author contributions

SB proposed the idea of producing this case report; MH conceived the outline of the article, collected the literature data, and drafted the manuscript; SL supervised and corrected the work; WN and HL contributed to the writing; HE, BEG, HM, and SB analyzed the whole article and checked the data. All authors read and approved the final version of the manuscript.

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### Availability of data and materials

Not applicable.

## Declarations

### Ethics approval and consent to participate

The clinical case was approved by our ethics committee. Informed consent has been obtained from the patient for publication of this case.

### Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

### Competing interests

The authors declare they have no competing interests.

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