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CASO CLÍNICO

Durable clinical benefit from osimertinib therapy in a lung adenocarcinoma patient with L718Q mutation in EGFR

Respuesta profunda y duradera en cáncer de pulmón con mutación L718Q en EGFR, adquirida después de la terapia con osimertinib

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Abstract

Actionable mutations in the epidermal growth factor receptor (EGFR) gene are prevalent in non-small cell lung cancer (NSCLC). The advent of targeted therapy using tyrosine kinase inhibitors (TKIs) has significantly improved patient outcomes. However, the eventual development of resistance poses a substantial challenge. Molecular profiling is essential for tailoring personalized treatment strategies. **Case Description:** A 61-year-old female patient with NSCLC harboring the L858R mutation in EGFR was initially treated with osimertinib, achieving a complete response. Nevertheless, at 26 months, the disease progressed with the emergence of the L718Q mutation in EGFR. Osimertinib was discontinued, and a regimen of chemoimmunotherapy combined with erlotinib was initiated. The patient achieved a second complete response and remained progression-free for 14 months. **Discussion:** The L718Q mutation is rare and confers resistance to osimertinib. However, as demonstrated in this case, the mutation may render the tumor susceptible to alternative treatments. Several case reports suggest modest efficacy with various drug combinations, including other TKIs, chemotherapy, and antiangiogenic agents. This case represents one of the longest progression-free survival periods reported in this context. This underscores the importance of re-evaluating molecular targets upon disease progression in EGFR-mutated non-small cell lung cancer (NSCLC).

Keywords: Carcinoma, Non-Small-Cell Lung; neoplasms; receptors, epidermal growth factor; mutation; chemoradiotherapy

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Resumen

Las mutaciones tratables en el gen del receptor del factor de crecimiento epidérmico (EGFR) son comunes en el cáncer de pulmón no microcítico (CPNM). La terapia dirigida con inhibidores de la tirosina quinasa (ITK) ha transformado los resultados, pero la resistencia plantea desafíos. El perfil molecular es crucial para el tratamiento personalizado. **Descripción del caso:** Una mujer de 61 años con CPNM mutado con L858R en EGFR respondió bien inicialmente a osimertinib. Sin embargo, en el mes 26, una biopsia confirmó progresión de la enfermedad con la aparición de la mutación L718Q. Se suspendió osimertinib y se inició quimioinmunoterapia con erlotinib. La paciente logró una supervivencia libre de progresión de 14 meses, demostrando la eficacia de la combinación. **Discusión:** Se analiza la rareza de la mutación L718Q después de osimertinib en primera línea y su impacto en la resistencia. Hay varios informes de casos que sugieren eficacia modesta con diferentes combinaciones de fármacos, incluyendo otros ITK, quimioterapia o antiangiogénicos. Este es uno de los periodos más largos de supervivencia libre de progresión reportados hasta ahora en este escenario. Además, este caso destaca la importancia de volver a realizar pruebas para objetivos moleculares al progresar en el CPNM mutado con EGFR.

Palabras clave: carcinoma de pulmón de células no pequeñas; neoplasias; factor de crecimiento epidérmico; mutación; quimioradioterapia.

Introduction

Actionable mutations in the epidermal growth factor receptor (EGFR) gene occur in 10-50% of non-small cell lung cancer (NSCLC) patients, depending on geographic location and ancestry [1]. The exon 19 deletion (ex19del) and the L858R mutation in exon 21 of EGFR are the most common mutations at diagnosis in patients with EGFR-mutated NSCLC (EGFRm, approximately 45% and 40%, respectively) [2]. Rare mutations, such as exon 20 insertions and other mutations in exons 18, 19, 20, and 21, are found in the remaining ~15% of cases [1]. In Colombia, EGFR mutations are present in 24 to 26% of new cases, possibly related to the country's Indigenous ancestry [3-5], The most common mutations are the exon 19 deletion and the exon 21 L858R mutation, occurring in 19% and 8% of cases, respectively [4].

Targeted therapy with tyrosine kinase inhibitors (TKIs) has revolutionized the prognosis for these patients, achieving unprecedented median overall survival compared to the previous standard of cytotoxic chemotherapy [6]. However, most patients develop new mutations that render them resistant to approved TKIs [1]. Currently, most guidelines recommend osimertinib as the first-line treatment for patients with common mutations in exons 19 and 21 [7, 8].

The mechanisms of resistance following first-line treatment with first or second-generation TKIs, such as gefitinib, erlotinib, and afatinib, differ from those observed with first-line treatment using osimertinib, a third-generation TKI. After the use of first and second-generation TKIs, most of resistance cases are attributed to acquired mutations or amplifications in EGFR, accounting for 50% of cases. These are known as mutations on-target [2]. The T790M mutation in exon 20 of EGFR is the most prevalent among these. In contrast, following the use of osimertinib, on-target mutations account for only 20-25% of resistance cases. Alterations in other genes, such as RET, ALK, BRAF, and HER2, among others, are more frequently observed in this scenario [2]. Among these mutations, the most significant are C797S, S768I, Ins20, G724S, G719S/C, L718Q, and compound mutations [2].

In the case of second-line treatment with osimertinib in patients with the T790M mutation,

the loss of this mutation appears to be one of the predominant mechanisms of resistance [9,10]. Acquired resistance to EGFR-targeting TKIs is largely explained by the initial tumor heterogeneity present at the onset of the disease. Within this heterogeneity, there are tumor subclones that are tolerant to the treatment and persist after its administration. When most of the tumor that is sensitive to the therapy is eliminated by the treatment, these resistant subclones proliferate, leading to disease progression [11]. Another prominent mechanism of resistance is the acquisition of new copy number alterations due to genomic instability [11].

Some guidelines recommend re-evaluating the molecular profile to identify potential therapeutic targets during disease progression. However, the utility of this approach is primarily documented in studies other than phase three clinical trials [7, 8]. Therefore, its use should be discussed with the patient and an interdisciplinary committee. When a new actionable mutation is not documented at the time of progression, the prognosis is poor, and therapeutic options are limited, primarily including chemotherapy, with or without immunotherapy [8]. However, it is increasingly clear that this latter option does not benefit EGFR-mutated tumors. This case shows the importance of searching for molecular targets during progression after anti-EGFR treatment to provide personalized therapy and improve the adverse prognosis of these patients.

Case report

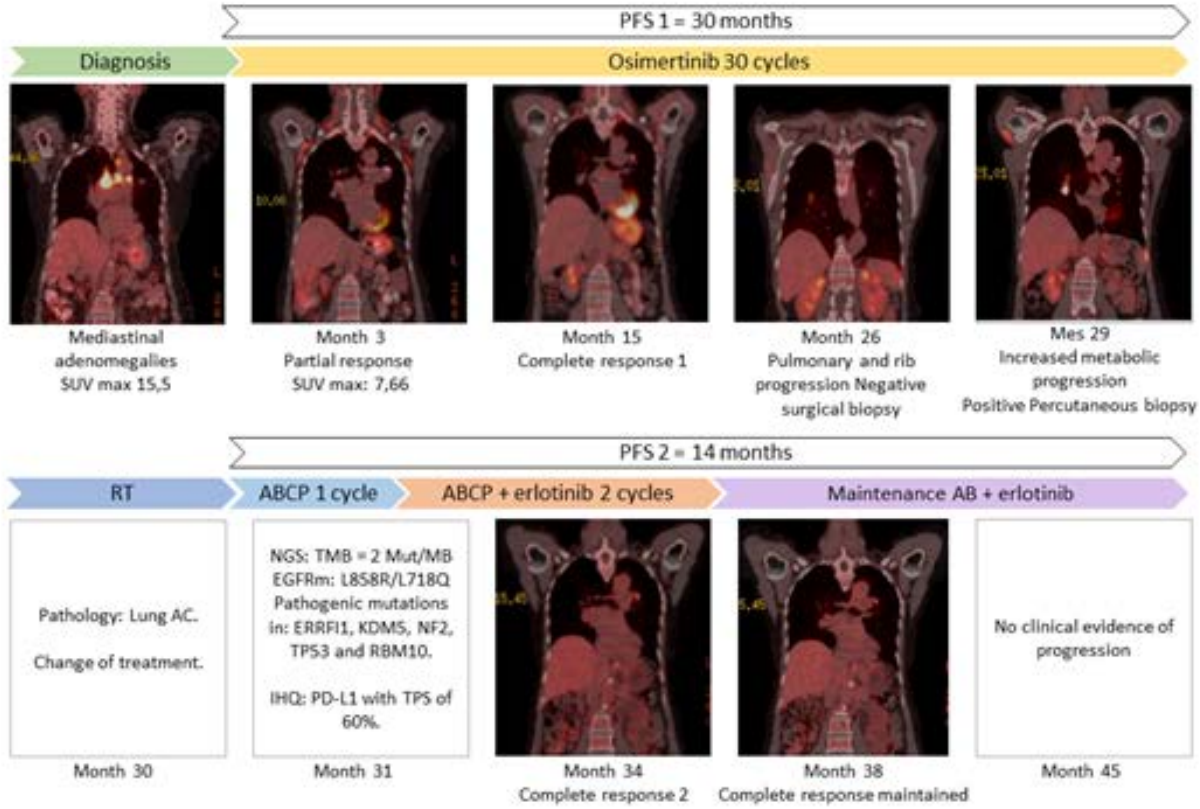
A 61-year-old female patient presented with respiratory symptoms. She had a medical history of hypertension, hysterectomy, and a bladder neurostimulator implant, with no prior tobacco use. At the initial institution, a chest computed tomography (CT) scan was performed (initial images not available), revealing a pulmonary nodule highly suspicious for malignancy. Consequently, a lobectomy and mediastinal staging were conducted. Pathological examination documented a 2 cm multifocal invasive adenocarcinoma with a 40% acinar pattern and 60% lepidic pattern, with negative resection margins. There was a lymphovascular invasion, involvement of the visceral and parietal pleura, one positive mediastinal lymph node at station V, and three lymph nodes at stations VIII and IX were free of tumor. Immunohistochemistry (IHC) showed reactivity for CK7, TTF1, and napsin in tumor cells. Molecular studies were negative for ALK rearrangements and positive for the L858R mutation in exon 21 of the EGFR gene.

The IHC study for programmed death-ligand 1 (PD-L1) using the 22C3 antibody (Dako pharmDx) resulted in a negative total proportion score (TPS <1%). A brain magnetic resonance imaging (MRI) was performed, which ruled out neoplastic involvement. Additionally, a positron emission tomography-computed tomography (PET-CT) scan revealed hypermetabolic adenopathies in the paratracheal, prevascular, precarinal, and subcarinal regions, which appeared malignant, as well as hypermetabolic involvement in the central face of the left parahilar area. The patient was assigned a stage IVA (T3N2M1A) according to the American Joint Committee on Cancer, eighth edition [12]. Treatment with osimertinib 80 mg daily was initiated, with good adherence and tolerance. After 3 months of treatment, a partial response was documented on the PET-CT, which further improved at 7 months. By 15 months, a complete morphological and metabolic response was achieved (Figure 1).

The patient maintained a complete response until the 26th month of treatment, at which point the PET-CT scan revealed a new hypermetabolic nodule in the superior segment of the right lower lobe and slight hypermetabolic lesions. A superior segmental lobectomy of the right lower lobe was performed, revealing a 6 mm nodule with no evidence of pleural lesions. The nodule was identified in the pathological examination

as a non-malignant intrapulmonary lymph node, and treatment with osimertinib was continued. At the 29th month of treatment, a PET-CT showed further progression in the right lung, along with new hypermetabolic lymph nodes located in the left internal mammary chain, right hilar region, and increased hypermetabolism of bone lesions. A percutaneous biopsy confirmed disease progression, with tumor cells showing reactivity for TTF1 and Napsin, while being negative for P40.

Figure 1.
Sequence of events, follow-up images, and treatments received by the patient.



Note: PFS 1= progression-free survival after the initiation of the first line. PFS 2= progression-free survival after the initiation of the second line. SUV max= maximum standardized uptake value in positron emission tomography. RT= radiotherapy. ABCP= atezolizumab plus bevacizumab plus carboplatin plus paclitaxel. AB= atezolizumab plus bevacizumab. AC= adenocarcinoma. TMB= tumor mutational burden. Mut/MB= mutations per megabase. EGFR= epidermal growth factor receptor. ERRFI1= ERBB receptor feedback inhibitor 1. KDM5= histone demethylase 5. NF2= neurofibromin 2. TP53= tumor protein P53. RBM10= RNA binding protein 10. IHC= immunohistochemistry. TPS= tumor proportion score (of PD-L1 expression). PD-L1= programmed death-ligand 1.

The administration of osimertinib was stopped in the patient after 30 months of treatment. Posteriorly, radiotherapy was administered to the rib lesions. At 31 months, a second line of chemoimmunotherapy was initiated with pemetrexed 500 mg/m², carboplatin with an area under the curve (AUC) of 6 mg/mL/min, atezolizumab 1200 mg, and bevacizumab 15 mg/kg every 21 days. Subsequently, a biopsy was performed for next-generation sequencing

(NGS) analysis, which revealed a tumor mutational burden (TMB) of 2 mutations per megabase, L718Q, and L858R mutations in EGFR, and additional mutations in the ERRFI1, KDM5, NF2, TP53, and RBM10 genes. The IHC for PD-L1 showed a TPS of 60%. Due to the finding of the L718Q mutation in EGFR, erlotinib was added to the chemoimmunotherapy regimen starting from the second cycle (32 months of treatment). A PET-CT was performed after 4 cycles of chemoimmunotherapy, documenting a second complete metabolic response, leading to maintenance therapy with erlotinib, atezolizumab, and bevacizumab. The patient has been followed up for 14 months without progression (Figure 1).

Discussion

This case demonstrates that a new molecular profiling upon progression after osimertinib therapy can open a range of additional therapeutic possibilities. If acquired resistance mutations are found on-target, there are multiple reports of efficacy with the use of combinations of two TKIs from different generations, combinations of TKIs with bevacizumab, or switching to a first or second-generation TKI, among others [12].

Resistance to osimertinib mediated by the mutation L718Q is relatively uncommon, as was reported in a subanalysis of the FLAURA trial. In this study patients were treated with first-line osimertinib and only 1% acquired the L718Q mutation at progression, while 6% acquired the C797X (13). In a sub-analysis of the AURA3 study, where osimertinib was used as a second-line treatment after progression on first-generation TKIs with the secondary T790M mutation, samples from 78 patients (94% of those included in the study) were analyzed. A low incidence of the L718Q mutation (n=1, ~1%) was also found, which was much lower than the frequency of the C797X mutation (n=14, 18%) [9]. These data contrast with real-world studies that show an incidence of 3.9% of secondary mutations at codon 718. Additionally, L718X seemed to develop preferentially in cancers that initially had the L858R mutation, being almost nonexistent in tumors that initially had the ex19del [10,13-14].

Mutations in exon 718 generate resistance to osimertinib because they directly affect the drug's binding site [1]. Some studies show that cancers with secondary mutations (i.e., L858R/L718Q acquired after first-line osimertinib) may retain their sensitivity to first and second-generation drugs but exhibit high resistance to third-generation drugs. In contrast, cells with tertiary mutations (i.e., L858R/T790M/L718Q acquired after second-line osimertinib) appear to be resistant to all three generations of TKIs [15-17]. Also, in a study with transgenic mice where the EGFRm L718Q gene was inserted into NSCLC cells, it was found that erlotinib does not individually inhibit this mutation, whereas afatinib does inhibit it [14].

Li et al., found 12 cases with the L718Q/V mutation in a systematic review and additionally reported two more cases from their own experience [18]. In one case, they found both L718Q/V mutations during progression on osimertinib, after which they used chemotherapy plus bevacizumab plus afatinib, without success. However, the subsequent reintroduction of osimertinib plus chemotherapy achieved a progression-free survival (PFS) of 4 months. In another case, the use of erlotinib after documenting the L718V mutation also failed to control the disease, and the patient passed away within a month. In their literature review, it was found that 11 out of 12 patients received an alternative TKI upon progression, with a median PFS of 2.6 months (ranging from 1 to 6 months). Partial responses were found with afatinib in only 3 of the 7 cases that received it. One of the two cases that received erlotinib did not respond, while the other had stable disease for 3 months. None of the cases treated with dacomitinib (n=3) or

anlotinib (n=1) experienced clinical benefit, and a complete response was not documented in any of the cases [18]. These data contrast with another case where dacomitinib achieved disease control for 6 months as monotherapy for tertiary L718Q after the use of osimertinib in the second line with the T790M mutation. Notably, NGS showed the coexistence of L858R and L718Q during progression, but not T790M [19].

Another strategy is described in the report by Song et al. where a patient was initially treated with icotinib. Upon progression, the T790M mutation was identified, and no response to osimertinib was achieved. Subsequent analysis revealed the coexistence of L718Q. Their strategy involved administering a few cycles of chemotherapy, which controlled the osimertinib-resistant clone and allowed for the reintroduction of the drug, achieving disease control for nearly 5 months after the emergence of the L718Q mutation [20]. The coexistence of multiple resistance mutations can further complicate the scenario, and the combination of different TKIs with monoclonal antibodies may lead to durable responses [21].

We found the coexistence of L858R/L718Q in our patient and decided to introduce erlotinib, following studies suggesting that such combination of mutations may retain sensitivity to first-generation TKIs. While the current literature review may support the use of afatinib in this scenario, none of the case reports have achieved a complete response or a progression-free survival (PFS) like that of our patient. This suggests that erlotinib may be a viable treatment strategy for the secondary L858R/L718Q mutation.

At the time we decided to initiate immunotherapy for our patient, the best evidence was based on the Impower150 study. This study reported that the combination of atezolizumab plus bevacizumab plus chemotherapy could benefit the subgroup of patients with anaplastic lymphoma kinase (ALK) rearrangements or EGFR mutations who had progressed on the TKIs available at that time [22]. However, more recent reports from phase 3 studies specifically designed to clarify the role of chemoimmunotherapy after progression on anti-EGFR TKIs contradict the results of Impower150. For example, Keynote-789 did not show any benefit in overall survival (OS) or progression-free survival (PFS) from the addition of pembrolizumab to platinum-based chemotherapy[23]. Similarly, the Impower151 study did not demonstrate a clear benefit of atezolizumab plus chemotherapy plus bevacizumab compared to chemotherapy plus bevacizumab [24]. On the other hand, the ATTLAS KCSG-LU19-04 study, which compared atezolizumab plus chemotherapy plus bevacizumab versus chemotherapy (without bevacizumab), found a modest but statistically significant benefit in progression-free survival (PFS) but not in overall survival (OS) with the addition of the antibodies, as well as a higher objective response rate[25]. In the ATTLAS study, subgroup analysis suggests a greater effect of the immunotherapy/anti-angiogenic/chemotherapy combination in patients with high PD-L1 expression (PD-L1 ≥ 50%). However, the number of patients in this subgroup is too small to draw definitive conclusions[25]. Additionally, the preliminary report from Keynote-789 did not report similar findings[26]. These data shows that, while immunotherapy does not play a role in these patients, bevacizumab might confer some benefit, but it is not conclusive. The results of these studies were reported after the treatment decision for our patient had been made.

The decision to continue immunotherapy in our patient was primarily based on the expression of PD-L1 > 50%. However, considering the most recent evidence, combinations with immunotherapy may not have a clear role in treating patients with EGFR-mutant non-small cell lung cancer (NSCLC) that has progressed on tyrosine kinase inhibitors (TKIs). As evident in our

patient, PD-L1 expression can vary significantly between initial presentation and recurrence due to temporal heterogeneity. The Impower151 and Keynote-798 studies have not yet been formally published, and it is unclear whether randomization stratification by PD-L1 expression was performed with progression tissue or initial diagnostic tissue, and whether the disease in progression still maintained EGFR alterations or if the resistance mechanism to TKIs was different. These questions may remain unanswered after the publication of these studies. Therefore, it cannot be stated that these factors influence the efficacy of immunotherapy in this context. In the case of our patient, with a high PD-L1 expression at progression, a deep and lasting response was achieved with the addition of bevacizumab and atezolizumab. However, we acknowledge that it is unclear whether the observed efficacy can be attributed to any individual component of the therapy or if all components were necessary.

In conclusion, this case demonstrates one of the longest progression-free survivals (PFS) reported in the literature following the development of the secondary L718Q mutation as a resistance mechanism to first-line osimertinib therapy in the context of the primary L858R mutation. These results were achieved with the combination of a first-generation TKI plus platinum-based chemotherapy, bevacizumab, and atezolizumab. It also highlights, along with other cases mentioned earlier, the increasingly clear importance of retesting for molecular targets after progression in EGFR-mutant NSCLC.

Ethics Committee

The ethics committee approved the publication. Consent for publication was granted by the patient.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Contributions

Contributors played a substantial role in conception, design, acquisition, analysis, interpretation, writing, and critical review of the manuscript. All authors approved the final content and accept responsibility for its accuracy and integrity.

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