Case Reports in Oncology

Case Rep Oncol 2019;12:625–630

DOI: 10.1159/000502214
Published online: August 6, 2019

Case Report

Triple Trouble: A Case of Multiple Resistance Mechanisms after First Generation EGFR-TKI in NSCLC

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Keywords
Resistance · EGFR · HER2 · Non-small cell lung cancer · Case report

Abstract
Epidermal growth factor receptor (EGFR)-targeted therapy has become standard of care in advanced stages EGFR-mutant non-small cell lung cancer. Acquired resistance to first-line EGFR-tyrosine kinase inhibitor (TKI) and subsequent disease progression is a common problem and mostly due to a secondary mutation (T790M) in EGFR. We report a case of a patient with EGFR-mutated lung adenocarcinoma who developed a complex resistance profile: T790M mutation, HER2 mutation and HER2 amplification after first-line EGFR-TKI. This patient was safely treated with a combination of osimertinib and trastuzumab and achieved a clinically meaningful and clear molecular response. This is the first reported case of acquired resistance to first-line EGFR-TKI based on three resistance mechanisms, treated with molecular targeted combination therapy.

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Introduction

Epidermal growth factor receptor (EGFR)-targeted therapy has become standard of care in advanced stages EGFR-mutant non-small cell lung cancer (NSCLC). However, most patients eventually develop disease progression due to acquired resistance to EGFR-tyrosine kinase inhibitor (TKI). A secondary mutation (T790M) in EGFR accounts for resistance in more than half of these cases. Other known resistance mechanisms include non-T790M secondary mutations in EGFR (1%), activation of parallel pathways mostly by HER2 amplification (10–15%) or MET amplification (5%), activating mutations in the common downstream pathway (1%), and phenotypic transformation (10%) [1].

Case Presentation

A 60-year-old male, never smoker, presented with cough and neck pain after which he was diagnosed with an EGFR-mutated (L858R) bone metastasized lung adenocarcinoma. Mutation and HER2 amplification analyses were carried out on diagnosis biopsy (Fig. 1). All mutation analyses in this case were performed by Next Generation Sequencing (TruSeq Custom Amplicon on MiSeq, 24 genes, Illumina) and all HER2 amplification analyses were performed by HER2 Fluoresence In Situ Hybridization (PathVysion HER2 DNA Probe Kit, Abbott). Our patient was treated with first generation EGFR-TKI gefitinib 250mg/day and this resulted in deep partial remission.

Six months after treatment initiation, disease progression occurred. Rebiopsy of the primary tumor revealed emergence of EGFR T790M resistance mutation (allele frequency 92%), HER2 S310Y mutation (allele frequency 32%) and HER2 amplification (HER2/CEP ratio 3.49), all not present at diagnosis (Fig. 2). After discussion on the multidisciplinary molecular pathology board, both T790M and HER2 alterations were considered to contribute to the emergence of resistance. Hence, second-line treatment with third generation EGFR-TKI osimertinib 80 mg/day in combination with HER2-receptor blocker trastuzumab (loading dose 4 mg/kg followed by 2 mg/kg weekly, off-label) was initiated and excellently tolerated. No signs of toxicity were noted, in particular no cardiotoxicity on routine echocardiography. This treatment resulted in disease stabilization.

Disease progression occurred four months later. Biopsy of pleural metastases showed persistence of EGFR L858R and T790M mutation (the latter at a lower allele frequency of 4%) and absence of HER2 mutation and amplification (Fig. 3). Treatment with osimertinib and trastuzumab was discontinued and platinum-based combination chemotherapy was initiated.

Discussion

In this case, we report the simultaneous presence of three resistance mechanisms (EGFR T790M mutation, HER2 S310Y mutation and HER2 amplification) after first-line EGFR-TKI treatment. Although multiple resistance mechanisms have already been identified, the simultaneous presence of these three resistance mechanisms is a unique feature. Moreover, the presence of HER2 mutation on top of HER2 amplification as resistance mechanism has not been reported before to our knowledge. Interestingly, the observed HER2 mutation is not the common HER2 exon 20 insertion, but an activating point mutation in the extracellular domain, that has been confirmed to be oncogenic both in vitro and in vivo [2–4].

The additional presence of HER2 alterations led to association of trastuzumab to osimertinib, as the principal pathway of resistance was unclear and the aim was to inhibit both EGFR and HER2 pathways. No such combination therapy for this resistance profile has been reported.

To date, experience with HER2 inhibition in HER2 mutated NSCLC is limited: case series suggest a response rate of 50% for trastuzumab in combination with chemotherapy and 18% for trastuzumab in combination with afatinib [5–8]. A recent phase II basket trial showed a response rate of 44% for emtansine-conjugated trastuzumab [9]. To date, there is no prospective evidence of trastuzumab alone or in combination with EGFR-TKI in HER2 mutated NSCLC.

In this case, treatment with osimertinib and trastuzumab was excellently tolerated and resulted in a clinically meaningful although not long-lasting stable disease. Interestingly, a clear molecular response was observed with disappearance of the HER2 mutated clone and HER2 amplification. Data about molecular response after HER2 inhibition are not available in previously published cases.

The course of this case should however be interpreted in the context of certain limitations. First, we cannot exclude that tumor heterogeneity rather than treatment is responsible for the observed molecular changes. Indeed, rebiopsy at the time of second progression was performed on pleural metastases rather than on the primary tumor because this was the predominant site of progression, and we have no liquid biopsy data for this particular case. Second, it is not impossible that osimertinib alone, which has also minor in vitro HER2 inhibitory effects [10], may have had the same molecular effect as the combination of osimertinib and trastuzumab. In this case, we combined osimertinib with trastuzumab, which is a far more potent HER2 inhibitor than osimertinib, assuming that maximal HER2 inhibition could lead to better clinical response. This remains of course unproven.

Conclusion

This is the first reported case of acquired resistance to first-line EGFR-TKI based on three resistance mechanisms. Second-line molecular based treatment with osimertinib and trastuzumab resulted in a clinically meaningful and clear molecular response in this patient. Targeting multiple (resistance) pathways might be a useful therapeutic option in patients with a complex EGFR resistance pattern and merits further investigation.

Acknowledgement

Not applicable.

Statement of Ethics

This research complies with the guidelines for human studies and was conducted in accordance with the World Medical Association Declaration of Helsinki. Written informed consent to publish was obtained and can be requested anytime.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no specific funding for this work.

Author Contributions

All authors (MR, BM, KP, JW and KC) contributed equally to this manuscript and approved the final manuscript.

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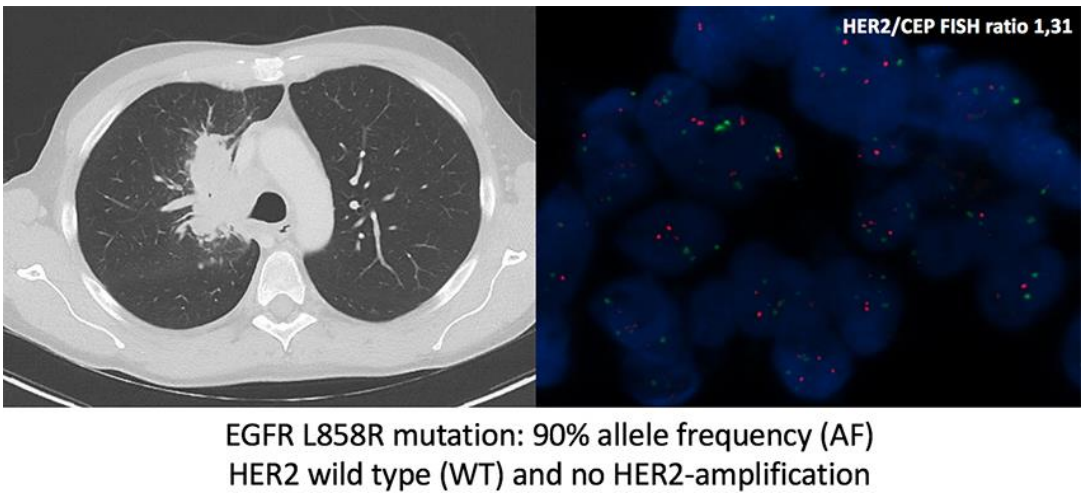

Fig. 1. Radiological and molecular status (HER2 FISH assay) at diagnosis.

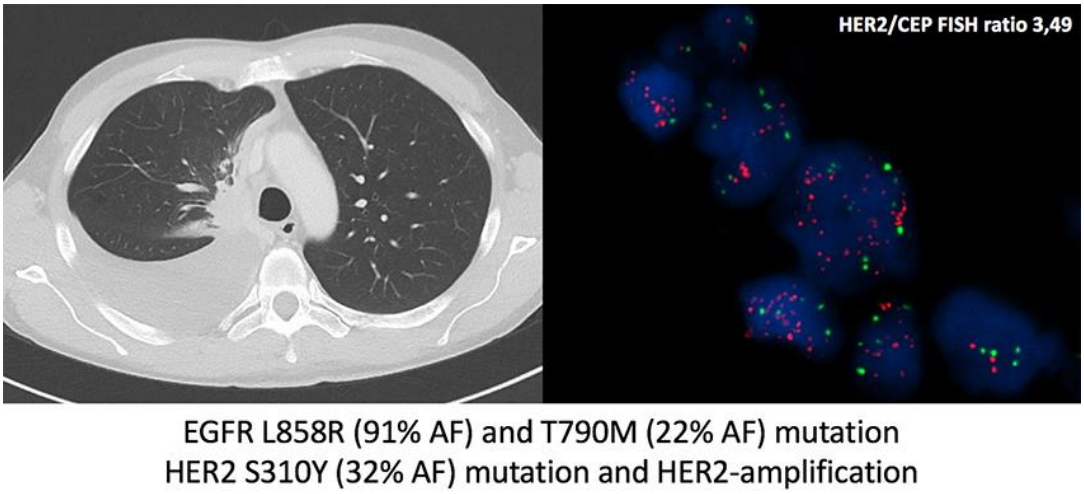

Fig. 2. Radiological and molecular (HER2 FISH assay) status at disease progression 6 months after the start of gefitinib.

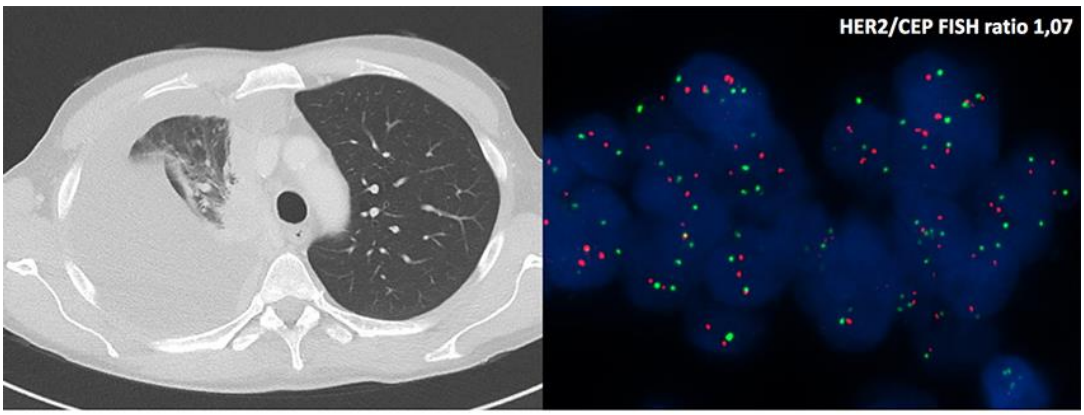

Fig. 3. Radiological and molecular (HER2 FISH assay) status at disease progression 4 months after the start of osimertinib and trastuzumab.