CASE REPORT

Combined therapy with osimertinib and afatinib in a lung adenocarcinoma patient with EGFR T790M mutation and multiple HER2 alterations after resistance to icotinib: A case report

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Abstract

Acquired resistance inevitably occurs after initial treatment with first-generation EGFR-tyrosine kinase inhibitors (TKIs). Several mechanisms have been identified, including EGFR T790M mutation and HER2 amplification. Herein, we present the case of a patient who progressed on first-generation EGFR-TKIs and developed EGFR T790M mutation, HER2 amplification, and HER2 mutation. The administration of single-agent osimertinib yielded an inconsistent response, with worsened pleural effusion and a reduction to lung metastases, but remarkably, a partial response was achieved after four weeks of treatment with combined osimertinib and afatinib, with grade 1 rash and grade 2 diarrhea. Our findings indicate an overlap of T790M, HER2 amplification, and HER2 mutation, which is rarely reported. Moreover, HER2 mutation was identified during the development of resistance, suggesting that HER2 mutation may cause resistance to first-generation EGFR-TKIs.

Introduction

HER2 alterations, including gene amplification, protein overexpression, and mutation, have been implicated as oncogenic drivers in lung cancers. HER2 amplification is identified as a resistance mechanism that occurs independently of EGFR T790M mutations, while HER2 mutations are thought to play a more significant role in lung tumorigenesis than overexpression or gene amplification, with promising efficacy of HER2 inhibitors. In this study, we describe the case of a patient who progressed on first-generation EGFR-TKIs and developed an EGFR T790M mutation, HER2 amplification, and HER2 mutation but achieved a remarkable response after combination treatment with osimertinib and afatinib.

Case report

A 57-year-old male smoker (40 pack-year) presented with a dry cough. A computed tomography (CT) scan revealed a mass in the inferior lobe of the right lung and multiple metastases in both sides. A bone scan also showed multiple metastases. A biopsy showed a lung adenocarcinoma. Biomarker analysis via Ventana immunohistochemistry and amplification refractory mutation system (ARMS) was negative for ALK rearrangement and exon 21 EGFR L858R mutation, respectively. First-line icotinib was commenced in April 2016 and a partial response was achieved until March 2017, with progression-free survival (PFS) of 11 months (Fig 1a). Liquid biopsy (super-ARMS) revealed the emergence of a T790M mutation, thus osimertinib was administered in May 2017. The patient experienced shortness of breath after a month of osimertinib treatment, with worsened pleural effusion but reduced lung metastases (Fig 1b). Next-generation sequencing (NGS)-based assay performed on DNA extracted from the pleural effusion and post-icotinib tumor tissues identified additional HER2 amplification and mutation in exon 20 V777L (Fig 2), while retrospective NGS showed no HER2 amplification or...
mutation in the pre-icotinib specimen. Continuous osimertinib treatment and a pleural injection of cisplatin were administered (Fig 1c) and a trend of progression was noted. Afatinib (30 mg daily) was added, and the patient achieved a partial response after four weeks of treatment, with mild toxicity (grade 1 rash and grade 2 diarrhea).

Discussion

EGFR-TKIs are recommended as first-line treatment for non-small cell lung cancer (NSCLC) patients harboring activating EGFR mutations. Despite the remarkable initial response, resistance to TKI eventually occurred in our patient who developed a T790M mutation within exon 20 of the TK domain of EGFR, which is the most common mutation. Other mechanisms were also identified, including HER2 amplification, which occurred independently of the EGFR T790M. Overlap among mechanisms of acquired resistance has been observed in 4% of 155 patients, and mainly consists of small cell histologic transformation with other mutations; only one patient had evidence of T790M and HER2 amplification in two different samples. In our case, the coexistence of T790M, HER2 amplification, and HER2 mutation was found in both the primary tumor and pleural effusion samples. Furthermore, the metastatic lesions responded to single-agent osimertinib, as well as the combination of osimertinib and afatinib, suggesting homogeneous resistance mechanisms in the primary tumor and metastatic lesions.

HER2 alterations, including gene amplification, protein overexpression, and mutation, have been implicated as oncogenic drivers in lung cancers. HER2 mutations are present in approximately 2% of NSCLC patients and consist of deletions, insertions, and missense mutations, which are often seen in women and non-smokers. HER2 mutations are thought to play a more significant role in lung tumorigenesis than overexpression or gene amplification via constitutive activation of the receptor and downstream AKT and MEK pathways. The majority of patients with HER2 amplified lung cancers

Figure 1 Computed tomography scans taken after (a) icotinib treatment showed a primary mass in the right inferior lobe and multiple metastases; (b) four weeks of osimertinib treatment showed a stable primary tumor, decreased metastases, and increased pleural effusion; (c) four months of osimertinib treatment; and (d) one month of combination osimertinib and afatinib treatment revealed a partial response and significantly improved pleural effusion.
are male and smokers.\textsuperscript{7} Re-biopsies in 155 patients resistant to EGFR-TKIs revealed no HER2 mutation, while 13\% of patients harbored HER2 amplification,\textsuperscript{1} suggesting that HER2 amplification is more significant than mutation in the development of acquired resistance to EGFR inhibitors. HER2 amplification and mutation may represent distinct molecular targets; therefore, different therapies are needed.\textsuperscript{7} HER2 mutation is predictive of sensitivity to HER2 inhibitors.\textsuperscript{1} Several studies and case series have reported responses to afatinib, dacomitinib, and trastuzumab in patients with HER2-mutant NSCLC,\textsuperscript{8–12} with the exception of a phase 2 study in which patients with HER2 insertion YVMA failed to respond to dacomitinib.\textsuperscript{11} However, for patients with HER2 gene amplification or overexpression, inconsistent efficacy results were observed from HER2-targeted antibodies, such as trastuzumab.\textsuperscript{13–15}

In this study, we present the first case of an overlap of T790M, HER2 amplification, and HER2 mutation. More-
complex mechanisms beyond HER2-amplification may have contributed to resistance in this patient.

To the best of our knowledge, this is the first time that the HER2 mutation has been detected in an NSCLC patient with acquired resistance to first-generation EGFR-TKIs, as well as the overlap of T790M, HER2 amplification, and HER2 mutation. We showed the efficacy of osimertinib and afatinib in overcoming multiple resistance from EGFR T790M and HER2 alterations. Greater understanding of how to overcome mechanisms of multiple resistance and the application of combined therapy may help to transform patient outcomes.

Disclosure
No authors report any conflict of interest.

Reference
1 Yu HA, Arcila ME, Rekhtman N et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 2013; 19: 2240–7.
2 Takezawa K, Pirazzoli V, Arcila ME et al. HER2 amplification: A potential mechanism of acquired resistance to egfr inhibition in EGFR-mutant lung cancers that lack the second-site EGFR-T790M mutation. Cancer Discov 2012; 2: 922–33.
3 Herter-Sprie GS, Greulich H, Wong K-K. Activating mutations in ERBB2 and their impact on diagnostics and treatment. Front Oncol 2013; 3: 1–10.
4 Kobayashi S, Boggon TJ, Dayaram T et al. EGFR mutation and resistance of non–small-cell lung cancer to Gefitinib. N Engl J Med 2005; 352: 786–92.
5 Arcila ME, Chaft JE, Nafa K et al. Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. Clin Cancer Res 2012; 18: 4910–8.
6 Garrido-Castro AC, Felip E. HER2 driven non-small cell lung cancer (NSCLC): Potential therapeutic approaches. Transl Lung Cancer Res 2013; 2: 122–7.
7 Li BT, Ross DS, Aisner DL et al. HER2 amplification and HER2 mutation are distinct molecular targets in lung cancers. J Thorac Oncol 2016; 11: 414–9.
8 Mar N, Vredenburgh JJ, Wasser JS. Targeting HER2 in the treatment of non-small cell lung cancer. Lung Cancer 2015; 87: 220–5.
9 Mazières J, Peters S, Lepage B et al. Lung cancer that harbors an HER2 mutation: Epidemiologic characteristics and therapeutic perspectives. J Clin Oncol 2013; 31: 1997–2003.
10 De Grève J, Teugels E, Geers C et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. Lung Cancer 2012; 76: 123–7.
11 Kris MG, Camidge DR, Giaccone G et al. Targeting HER2 aberrations as actionable drivers in lung cancers: Phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. Ann Oncol 2015; 26: 1421–7.
12 Cappuzzo F, Bemis L, Varella-Garcia M. HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer. N Engl J Med 2006; 354: 2619–21.
13 Gatzemeier U, Groth G, Butts C et al. Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer. Ann Oncol 2004; 15: 19–27.
14 Lara PN, Laptalo L, Longmate J et al. Trastuzumab plus docetaxel in HER2/neu-positive non-small-cell lung cancer: A California cancer consortium screening and phase II trial. Clin Lung Cancer 2004; 5: 231–6.
15 Langer CJ, Stephenson P, Thor A, Vangel M, Johnson DH, Eastern Cooperative Oncology Group Study 2598. Trastuzumab in the treatment of advanced non-small-cell lung cancer: Is there a role? Focus on eastern cooperative oncology group study 2598. J Clin Oncol 2004; 22: 1180–7.