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CASE REPORT

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Non-small-cell lung cancer with ERBB2 mutation in non-tyrosine kinase domain benefits from pyrotinib: A case report

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Abstract

Tyrosine kinase domain (TKD) mutation and particularly exon 20 insertion mutations of erb-b2 receptor tyrosine kinase 2 (ERBB2/HER2) have been extensively reported in non-small cell lung cancer (NSCLC). Nevertheless, the clinical significance of non-TKD mutations remains unknown. To date, no clinical trials have revealed that tyrosine kinase inhibitors are effective in NSCLC patients with non-TKD ERBB2 mutations. Here we report a patient with advanced lung adenocarcinoma harboring non-TKD mutation of ERBB2, S335C, without other actionable alterations benefited from pyrotinib. After first-line treatment of pyrotinib monotherapy, a pan-HER inhibitor, the patient achieved a durable partial response with good tolerance. This case powerfully illustrates that pyrotinib might be a promising first-line treatment strategy for NSCLC patients with non-TKD mutation of ERBB2.

KEYWORDS

ERBB2, non-small cell lung cancer, nontyrosine kinase domain mutation, pyrotinib, targeted therapy

INTRODUCTION

Epidermal growth factor receptor (EGFR) started the era of targeted therapy for the EGFR-mutated non-small cell lung cancer (NSCLC) population.[1] With continuous easier accessibility of next-generation sequencing (NGS), more and more oncogenic mutations have become the targets for NSCLC treatment, and the survival of NSCLC patients is continually improving.[2–8] A previous study reported that in over 60% of patients with lung adenocarcinomas with detected driver mutations, 9–14% were rare driver mutations.[9] Among them, erb-b2 receptor tyrosine kinase 2 (ERBB2, also known as HER2) mutations have been detected in approximately 1–3% of NSCLC patients,[10,11] which was up to 4.5% with the easier accessibility of NGS.[12]

ERBB2 is a transmembrane receptor tyrosine kinase of the epidermal growth factor receptor family, whose ligand binding to the EGFR (HER1), HER3, and HER4 extracellular domains catalyzes the formation of homodimers and heterodimers, which in turn actives downstream signaling cascade such as the PI3K and MAPK pathways.[13] ERBB2 has been extensively studied in breast cancer. Its overexpression or gene amplification is an important biomarker in breast cancer and is associated with improved prognosis with use of HER2-targeting drugs (trastuzumab, lapatinib, pertuzumab, and adotrastuzumab emtansine [T-DM1]).[14] In NSCLC, ERBB2 mutation was more prevalent than amplification or overexpression.[15,16] Conventional EGFR-targeting drugs are not effective against ERBB2 mutations in NSCLC. It is necessary to explore effective targeted therapies for patients with advanced NSCLC harboring HER2 mutations.

A775_Y776insYVMA (alternative nomenclature p.Y772_A775dup), G776delinsVC, G778_P780dup, and S310F are the most common ERBB2 mutations in NSCLC.[12,17,18] However, most of the current studies focused on mutations within the tyrosine kinase domain (TKD), mainly A775_Y776insYVMA in exon20, but ignored oncogenic mutation outside the TKD.[10,11] Several pan-HER inhibitors, such as afatinib,[17–19] dacomitinib,[20] neratinib,[21] and pyrotinib,[22] have been investigated among NSCLC patients with ERBB2 mutation of A775_Y776insYVMA. However, none of these studies involved non-TKD mutations of ERBB2. Here we

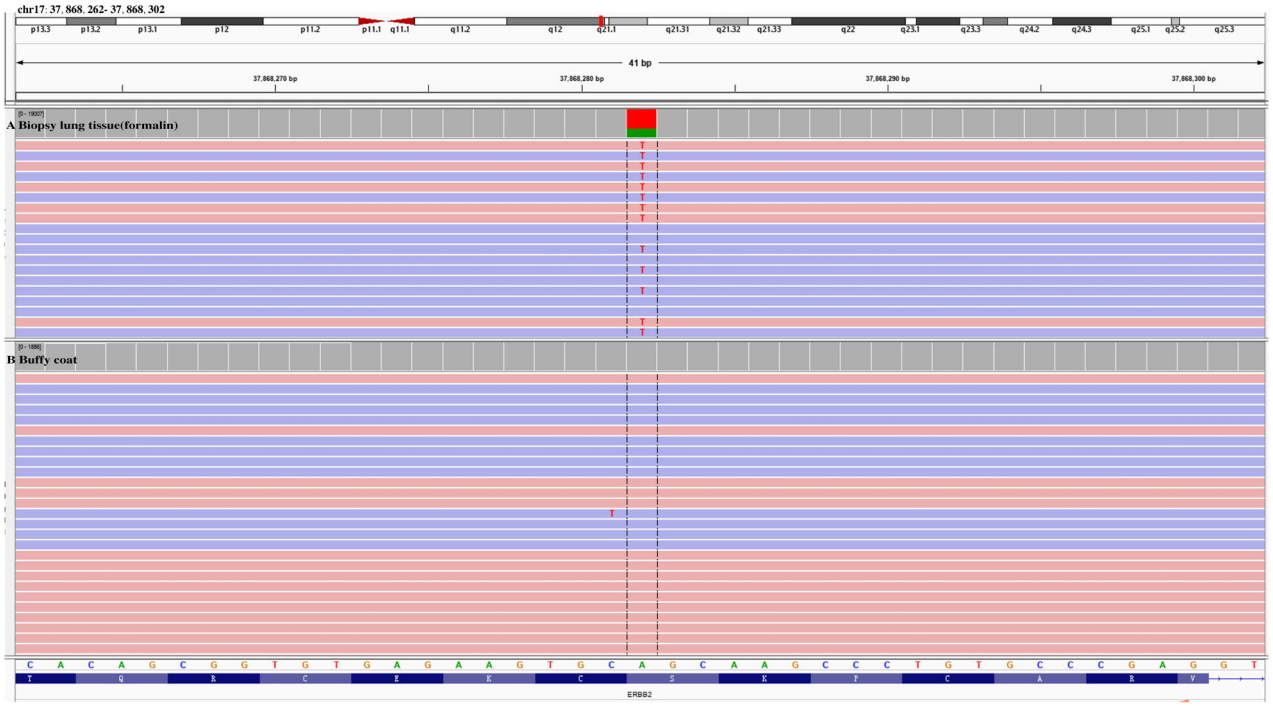

FIGURE 1 Identification of ERBB2 S335C mutation using next-generation sequencing shown by the integrative genomics viewer (IGV)

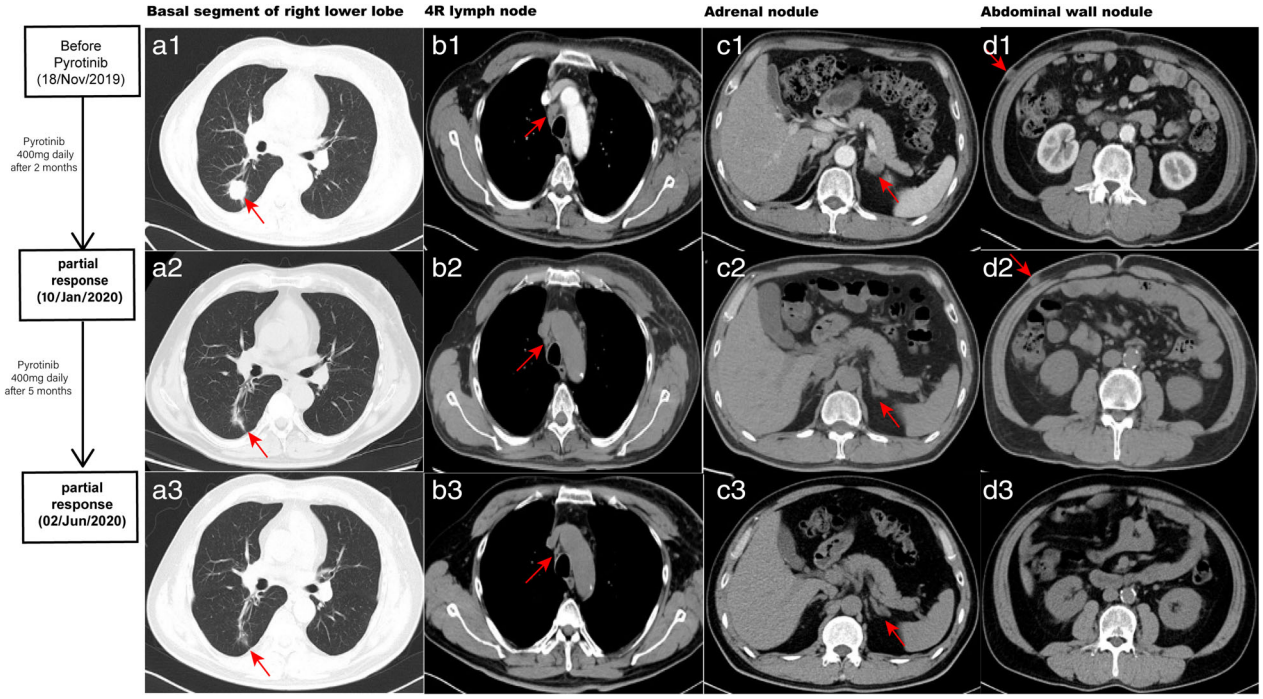

FIGURE 2 Computed tomography scans of the patient before pyrotinib and follow-up after pyrotinib treatment. Red arrows highlight the targeted lesions

demonstrate the case of a lung adenocarcinoma patient harboring non-TKD mutation of ERBB2, who was successfully treated by pyrotinib, indicating that pyrotinib might be a promising therapy for non-TKD mutation of NSCLC.

Case presentation

A 50-year-old male (non-smoker) presented with developed irritable cough and a right lower lobe mass in November 2019. Chest-abdomen contrast enhancement computed

tomography (CT) demonstrated right lower lobe mass (2.8 × 2.8 cm), right supraclavicular lymph node enlargement, mediastinal and right hilar lymph node enlargement, left adrenal nodules, and soft tissue nodules under the anterior abdominal wall (Figure 1). Pathology of lung biopsy revealed poorly differentiated adenocarcinoma. The biopsy of the left supraclavicular lymph node was similar to the lung adenocarcinoma, confirming metastatic disease (cT1cN3M1c, stage IVb). Subsequently, NGS of the lung mass revealed an ERBB2 S335C mutation (Figure 1). Based on the oncogenic driver mutation and drug accessibility, treatment of pyrotinib 400 mg daily was started from December 2019. In March 2020, images showed partial response with 70% tumor shrinkage in the lung and metastasis lymph nodes that was ongoing (last follow-up 2 December 2020) (Figure 2). Fortunately, the patient endured grade 1 diarrhea without other adverse events during treatment.

DISCUSSION

With the discovery of driver mutations such as EGFR and the development of tyrosine kinase inhibitor (TKI) therapies targeting these mutations, the treatment of NSCLC has moved from conventional chemotherapy to targeted therapies. ERBB2 mutations are found in approximately 1–3% of NSCLC patients.[10,11,23] With easier accessibility of NGS, the prevalence of ERBB2 mutations was up to 4.5%.[12] A775_Y776insYVMA (alternative nomenclature p.Y772_A775dup), G776delinsVC, G778_P780dup, and S310F are the most recurrent ERBB2 mutations in NSCLC,[12,17,18] and A775_Y776insYVMA is the hotspot.

The biological function of the mutant domain determines its carcinogenic ability and the choice of subsequent treatment drugs. Highly oncogenic mutations are observed in the furin-rich cysteine domain, which are involved in the formation of disulfide bonds with other ErbB family members to format homodimers and heterodimers. For example, S310F causes C-terminal phosphorylation, and a disulfide bond replaces the cysteine-linked dimer in the region.[24]

At present, clinical activity has been observed with several ERBB2-targeted tyrosine kinase inhibitors in patients with advanced lung cancer. However, none of them involved in non-TKD domain mutations of ERBB2. Studies of ERBB2 antibody-drug conjugates, such as Ado-trastuzumab(T-DM1)[25] and trastuzumab deruxtecan (T-DXd, DS-8201a),[26,27] confirmed the effectiveness against non-TKD mutations. To date, there has been no clinical evidence revealing the clinical benefit of ERBB2-targeted tyrosine kinase inhibitor monotherapy for lung cancer patients who harbor non-TKD mutation.

Pyrotinib is an irreversible TKI targeting ERBB. Zhou et al[14] reported that the efficacy of pyrotinib among NSCLC patients harboring ERBB2 exon 20 insertion mutations with an ORR of 53.5% and a median progressive-free survival (PFS) of 6.4 months. In this work, pyrotinib demonstrated promising antitumor activity targeted to non-TKD domains of ERBB2 such as S335C, with good tolerance. Additional analysis of large clinical data and trials are needed to provide accurate insight of ERBB2-mutated therapy.

CONCLUSION

Non-TKD mutations of ERBB2 are promising targest for tyrosine kinase inhibitors. Pyrotinib might be an potential treatment for patients with NSCLC harboring non-TKD domains mutations of ERBB2.

DISCLOSURE

The authors report no conflict of interest in this work.

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