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. 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. A previous study reported that in over 60% of patients with lung adenocarcinomas with detected driver mutations, 9–14% were rare driver mutations. Among them, erb-b2 receptor tyrosine kinase 2 (ERBB2, also known as HER2) mutations have been detected in approximately 1–3% of NSCLC patients, which was up to 4.5% with the easier accessibility of NGS. 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. 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 adotrastuzumub emtansine [T-DM1]). In NSCLC, ERBB2 mutation was more prevalent than amplification or overexpression. 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. 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. Several pan-HER inhibitors, such as afatinib, dacomitinib, neratinib, and pyrotinib, 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...
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 (cT4cN3M1c, 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. 

With easier accessibility of NGS, the prevalence of ERBB2 mutations was up to 4.5%. A775_Y776insYVMA (alternative nomenclature p.Y772_A775dup), G776delinsVC, G778_P780dup, and S310F are the most recurrent ERBB2 mutations in NSCLC,

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.

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) and trastuzumab deruxtecan (T-DXd, DS-8201a), 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. 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 targets for tyrosine kinase inhibitors. Pyrotinib might be a 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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REFERENCES

1. Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriramanpong V, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol. 2011;29(21):2866–74.
2. Awad MM, Oxnard GR, Jackman DM, Savukoski DO, Hall D, Shivdasani P, et al. MET exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and c-met overexpression. J Clin Oncol. 2016;34(7):21–30.
3. Drilon A, Rekhtman N, Arcila M, Wang L, Ni A, Albano M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-Centre, phase 2, single-arm trial. Lancet Oncol. 2016;17(12):1653–60.
4. Lee SH, Lee JK, Ahn MJ, Kim DW, Sun JM, Keam B, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer harboring RET rearrangement: a phase II clinical trial. Ann Oncol. 2017;28(2):292–7.
5. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus Crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. 2018;378(8):731–8.
6. Girard L, Camidge DR, Kim HR, Lee JS, Xie H, Min YJ, et al. Cabozenib in patients with advanced non-small-cell lung cancer: an open-label, single-Centre, phase 2, single-arm trial. J Clin Oncol. 2016;34(7):21–30.
7. Planchard D, Smit EF, Groen HJM, Mazieres I, Besse B, Holland À, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol. 2017;18(10):1307–16.
8. Drilon A, Laetsch TW, Kummer S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of Larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 2018;378(8):731–9.
9. Oxnard GR, Binder A, Jänne PA. New targetable oncogenes in non-small-cell lung cancer. J Clin Oncol. 2013;31(8):1097–104.
10. Arcila ME, Chaft JE, Nafa K, Roy-Chowdhuri S, Lau C, Zaidinski M, et al. Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. Clin Cancer Res. 2012;18(18):4910–8.
11. Suzuki M, Shiraishi K, Yoshida A, Shimada Y, Suzuki K, Asamura H, et al. HER2 gene mutations in non-small cell lung carcinomas: concurrence with Her2 gene amplification and Her2 protein expression and phosphorylation. Lung Cancer. 2015;87(1):14–22.

12. Wei XW, Gao X, Zhang XC, Yang JJ, Chen ZH, Wu YL, et al. Mutational landscape and characteristics of ERBB2 in non-small cell lung cancer. Thorac Cancer. 2020;11(6):1512–21.

13. Normanno N, Bianco C, De Luca A, Maiello MR, Salomon DS. Target-based agents against ErbB receptors and their ligands: a novel approach to cancer treatment. Endocr Relat Cancer. 2003;10(1):1–21.

14. Zhou C, Li X, Wang Q, Gao G, Zhang Y, Chen J, et al. Pyrotinib in HER2-mutant advanced lung adenocarcinoma after platinum-based chemotherapy: a multicenter, open-label, single-arm, phase II study. J Clin Oncol. 2020;38:2753–61.

15. Perera SA, Li D, Shimamura T, Raso MG, Ji H, Chen L, et al. HER2YVMA drives rapid development of adenosquamous lung tumors in mice that are sensitive to BBW2992 and rapamycin combination therapy. Proc Natl Acad Sci U S A. 2009;106(2):474–9.

16. Shimamura T, Ji H, Minami Y, Thomas RK, Lowell AM, Shah K, et al. Non-small-cell lung cancer and Ba/F3 transformed cells harboring the ERBB2 G776insV_C/G/C mutation are sensitive to the dual-specific epidermal growth factor receptor and ERBB2 inhibitor HKI-272. Cancer Res. 2006;66(13):6487–91.

17. Mazieres J, Peters S, Lepage B, Cortot AB, Barlesi F, Beau-Faller M, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol. 2013;31(16):1997–2003.

18. Liu Z, Wu L, Cao J, Yang Z, Zhou C, Cao L, et al. Clinical characterization of ERBB2 exon 20 insertions and heterogeneity of outcomes responding to afatinib in Chinese lung cancer patients. Onco Targets Ther. 2018;11:7323–31.

19. Fang W, Zhao S, Liang Y, Yang Y, Yang L, Dong X, et al. Mutation variants and co-mutations as genomic modifiers of response to Afatinib in HER2-mutant lung adenocarcinoma. Oncologist. 2020;25(3):e545–54.

20. Kris MG, Camidge DR, Giaccone G, Hida T, Li BT, O’Connell J, 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(7):1421–7.

21. Ogoshi Y, Shien K, Yoshiooka T, Torigoe H, Sato H, Sakaguchi M, et al. Anti-tumor effect of neratinib against lung cancer cells harboring HER2 oncogene alterations. Oncol Lett. 2019;17(3):2729–36.

22. Wang Y, Jiang T, Qin Z, Jiang J, Wang Q, Yang S, et al. HER2 exon 20 insertions in non-small-cell lung cancer are sensitive to the irreversible pan-Her receptor tyrosine kinase inhibitor pyrotinib. Ann Oncol. 2019;30(3):447–55.

23. Liu Y, Purvis J, Shih A, Weinstein J, Agrawal N, Radhakrishnan R. A multiscale computational approach to dissect early events in the Erb family receptor mediated activation, differential signaling, and relevance to oncogenic transformations. Ann Biomed Eng. 2007;35(6):1012–25.

24. Greulich H, Kaplan B, Mertins P, Chen TH, Tanaka KE, Yun CH, et al. Functional analysis of receptor tyrosine kinase mutations in lung cancers identify oncogenic extracellular domain mutations of ERBB2. Proc Natl Acad Sci U S A. 2012;109(36):14476–81.

25. Li BT, Shen R, Buonocore D, Olah ZT, Ni A, Ginsberg MS, et al. Ado- Trastuzumab Emtansine for patients with HER2-mutant lung cancers: results from a phase II basket trial. J Clin Oncol. 2018;36(24):2532–7.

26. Tsurutani J, Iwata H, Krop I, Jänecke PA, Doi T, Takahashi S, et al. Targeting HER2 with Trastuzumab Deruxtecan: a dose-expansion, phase I study in multiple advanced solid tumors. Cancer Discov. 2020;10(5):674–87.