

Case Report

Successful Treatment of Afatinib-Refractory Non-Small Cell Lung Cancer with Uncommon Complex EGFR Mutations Using Pembrolizumab: A Case Report

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Keywords

Afatinib · EGFR uncommon mutation · Immune-checkpoint inhibitor · Non-small-cell lung cancer · Pembrolizumab

Abstract

Although there has been significant progress in immune-checkpoint inhibitor (ICI) treatment, it remains controversial whether they should be used in the treatment of epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC). We herein report the case of an NSCLC patient with uncommon complex EGFR mutations (G719S and L861Q) who was refractory to afatinib treatment but who showed a good response to pembrolizumab treatment. A 65-year-old female ex-smoker was diagnosed with right upper lobe NSCLC (clinical stage IVB; cT2bN3M1c). She had received afatinib for two months, but her disease showed rapid progression. Pembrolizumab treatment was initiated because more than 75% of her tumor cells expressed PD-L1. Her tumor responded well to pembrolizumab treatment and it remained effective for more than 1 year. Our case suggests that pembrolizumab treatment is a treatment option for NSCLC patients with uncommon EGFR mutations and high PD-L1 expression levels who are refractory to EGFR-TKI treatment.

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Introduction

Over the past few years, the development of immune checkpoint inhibitors (ICIs) has represented a major breakthrough in the treatment of advanced non-small-cell lung cancer (NSCLC). Pembrolizumab, a humanized monoclonal antibody that blocks programmed death-1 (PD-1), has become the standard of care as a first-line chemotherapy for advanced NSCLC when over 50% of tumor cells are positive for PD-L1 [1], and pembrolizumab combined with platinum-based chemotherapy has also become a first-line treatment option [2]. Despite these major developments, the usefulness of ICIs in the treatment of epidermal growth factor receptor (EGFR)-mutated NSCLC is still uncertain.

For NSCLC patients with sensitizing EGFR mutations, ICIs are less effective and treatment with EGFR-tyrosine kinase inhibitors (TKIs) is the standard of care. However, not all patients with EGFR mutations show a good response to EGFR-TKIs. Uncommon EGFR mutations, such as substitutions in exon 18 (i.e., G719X, E790K/E790A), insertions and/or point mutations in exon 20 (i.e., S768I), insertions in exon 19, and mutations in exon 21 (i.e., L861Q) account for approximately 10% of all EGFR mutations [3]. EGFR-TKIs showed inferior efficacy in the treatment of cancers with these uncommon EGFR mutations than in cancers with common mutations (exon 19 deletion and L858R). Considering the poor response to EGFR-TKIs, the establishment of other treatments is required for patients with uncommon EGFR mutations.

We herein report the case of an NSCLC patient with uncommon EGFR mutations in whom first-line treatment with afatinib failed but second-line treatment with pembrolizumab was successful.

Case Presentation

A 65-year-old female ex-smoker presented to the otolaryngology department of our hospital with a 1 cm nodule on her tongue. Fine needle aspiration (FNA) of the tongue tumor only showed atypical cells. She was referred to our department after a CT scan showed a solitary tumor on the right upper lobe of her lung (Fig. 1A). Bronchial fibroscopy revealed that the right B1 was obstructed by a tumor, which was diagnosed as non-small cell carcinoma. Immunohistochemical staining showed that the tumor was negative for TTF-1/ p40/ CK7, and EGFR mutations were detected in exon 18 (G719S) and exon 21 (L861Q) by the PNA-LNA PCR Clamp method. On immunohistochemical staining of PD-L1 (IHC 22C3), more than 75% of the tumor cells were positively stained. Metastasis to the right mediastinal, hilar, and subclavian lymph node, and left adrenal gland was suspected based on PET-CT, and a metastatic lesion of 4.5 mm in diameter was found on the right frontal lobe by head MRI. Based on these findings, the diagnosis was cT2bN3M1c (ADR, BRA, LYM, OTH) stage IVB.

Although afatinib 30mg/day was initiated, the primary nest and lymph node metastasis all progressed within 2 months (Fig. 1B). We discontinued afatinib and switched to pembrolizumab. The patient's disease responded well to pembrolizumab treatment, which has continued to be effective for more than 1 year without serious side effects (Fig. 1C).

Discussion

EGFR mutations are detected in approximately 40–60% in East Asians and approximately 10% of Caucasians. Exon 19 deletion and exon 21 L858R mutation (common sensitising

mutations) account for 45–50% and 40–45% of these mutations, respectively, while single or uncommon complex mutations account for 2.6–14% of mutations [4]. Since the randomized phase III IPASS (Iressa Pan Asian Study), EGFR-TKI has been established as a first-line chemotherapy for EGFR-mutant NSCLC; however, it tends to be less effective in treating patients with uncommon EGFR mutations [3, 5]. Afatinib, the second-generation EGFR-TKI, is considered to be more effective than first-generation TKIs, because it is an irreversible inhibitor that unbinds the high binding affinity of these mutations to ATP [6]. The patient in the present case report, who had uncommon and complex EGFR mutations (G719S+L861Q), showed rapid progression without a response during two months of treatment with afatinib.

A subgroup analysis of 3 randomized trials revealed that immune-checkpoint inhibitors are usually less effective than docetaxel in the treatment of NSCLC with oncogenic driver mutations [7, 8]. However, we cannot fully give up on ICIs in the treatment of patients with EGFR mutations because some patients with EGFR mutations have shown long survival on PD-1 inhibitors. In fact, a recently reported phase III study demonstrated that patients with EGFR mutations who received atezolizumab combined with carboplatin, paclitaxel and bevacizumab chemotherapy showed better PFS in comparison to those who received chemotherapy alone [9]. The only two recently published studies pointed out the possibility that uncommon EGFR mutations may be associated with the efficacy of ICIs to EGFR-mutant NSCLC [10, 11]. Yoshida H et al. reported that a history of heavy smoking (smoking index >30 pack-years), a shorter duration of response to EGFR-TKI therapy, and the existence of uncommon EGFR mutations are factors that predict the efficacy of nivolumab in EGFR-mutant NSCLC [10]. Yamada et al. concluded that uncommon mutations without T790M mutation are associated with a good response to ICIs [11]. As in previously reported cases, our patient responded well to pembrolizumab treatment. Immune checkpoint inhibitors may be an option for the subsequent treatment of NSCLC patients with uncommon EGFR mutations with treatment failure on EGFR-TKIs.

Conclusion

We reported a case of NSCLC with uncommon complex EGFR mutations (G719S+L861Q) in which a significant response to the second-line treatment with pembrolizumab was observed after the failure of first-line treatment with afatinib. Pembrolizumab might be a treatment option for NSCLC patients with uncommon EGFR mutations and the high expression of PD-L1 who are refractory to EGFR-TKI treatment.

Statement of Ethics

The authors have no ethical conflicts to disclose. Written informed consent was obtained from our patient for publication of this case report.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

- 1 Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csósz T, Fülöp A, et al.; KEYNOTE-024 Investigators. Pembrolizumab versus Chemotherapy for PD-L1 positive Non-small-cell lung cancer. *N Engl J Med*. 2016 Nov;375(19):1823–33.
- 2 Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al.; KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018 May;378(22):2078–92.
- 3 Russo A, Franchina T, Ricciardi G, Battaglia A, Picciotto M, Adamo V. Heterogeneous responses to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with uncommon EGFR mutations: new insights and future perspectives in this complex clinical scenario. *Int J Mol Sci*. 2019 Mar;20(6):1431.
- 4 Yang JC, Sequist LV, Geater SL, Tsai CM, Mok TS, Schuler M, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol*. 2015 Jul;16(7):830–8.
- 5 Kate S, Chougule A, Joshi A, Noronha V, Patil V, Dusane R, et al. Outcome of uncommon EGFR mutation positive newly diagnosed advanced non-small cell lung cancer patients: a single center retrospective analysis. *Lung Cancer (Auckl)*. 2019 Jan;10:1–10.
- 6 Park K, Wan-Teck Lim D, Okamoto I, Yang JC. First-line afatinib for the treatment of EGFR mutation-positive non-small-cell lung cancer in the ‘real-world’ clinical setting. *Ther Adv Med Oncol*. 2019 Apr;11:1758835919836374.
- 7 Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al.; OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017 Jan;389(10066):255–65.
- 8 Bylicki O, Paleiron N, Margery J, Guisier F, Vergnenegre A, Robinet G, et al. Targeting the PD-1/PD-L1 immune checkpoint in EGFR-mutated or ALK-translocated non-small-cell lung cancer. *Target Oncol*. 2017 Oct;12(5):563–9.
- 9 Rock M, Socinski MA, Cappuzzo F, et al; LBA1_PR Primary PFS and safety analysis of a randomized phase III study of carboplatin + paclitaxel +/- bevacizumab, with or without atezolizumab in 1L non-squamous metastatic nslc (IMPOWER150). *Ann Oncol*. 2017 Dec;28(suppl_11):mdx760.002.
- 10 Yamada T, Hirai S, Katayama Y, Yoshimura A, Shiotsu S, Watanabe S, et al. Retrospective efficacy analysis of immune checkpoint inhibitors in patients with EGFR-mutated non-small cell lung cancer. *Cancer Med*. 2019 Apr;8(4):1521–9.
- 11 Yoshida H, Kim YH, Ozasa H, Nagai H, Sakamori Y, Tsuji T, et al. Nivolumab in non-small-cell lung cancer with EGFR mutation. *Ann Oncol*. 2018 Mar;29(3):777–8.



Fig. 1. Chest CT at the time of the diagnosis (A), at two months after afatinib treatment (B), and at one year after pembrolizumab treatment (C).