Durable Response to Immunotherapy Plus Chemotherapy in a Patient With Untreated, Brain-metastatic, EGFR Exon 20 Insertion Mutation Lung Adenocarcinoma

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Abstract

Epidermal growth factor receptor (*EGFR*) 20 exon insertion is the second most common *EGFR* aberrations in non-small cell lung cancer (NSCLC). Despite some novel *EGFR* inhibitors showing encouraging antitumor activity, clinically obtainable management for this subset of patients remains an unmet need. Although immune checkpoint inhibitors (ICIs) have led to unprecedented clinical benefit in metastatic NSCLC, clinical evidence suggests that *EGFR* mutant lung cancers rarely derive benefit from treatment with ICIs. We report that a lung adenocarcinoma patient harboring an actionable gene mutation of *EGFR* exon 20 insertion, high PD-L1 expression, high tumor mutational burden, as well as alterations in immune-related genes including *CTNNB1* (Catenin β 1) S37F and *ARID2* (AT-rich interactive domain-containing protein 2) E1056X responded to upfront PD-1 inhibitor plus chemotherapy. As an advanced-stage lung cancer with brain metastases indicating poor prognosis, the patient achieved an unusual and durable response over 15 months. Upfront ICIs plus chemotherapy might be an option for some NSCLC patients harboring *EGFR* exon 20 insertion mutation. Further study is needed to validate the predictor involved in responders to ICIs-based therapy with *EGFR* mutations.

Introduction

Programmed cell death-1 (PD-1)/programmed cell death-ligand 1(PD-L1) immune checkpoint inhibitors (ICIs), alone or in combination with chemotherapy, have revolutionized the standard treatment for non-small-cell lung cancer (NSCLC), bringing unprecedented durable clinical benefit to late-stage patients. Despite this, a portion of patients displays only modest responses or remains unresponsive[1, 2]. Increasing evidence indicates epidermal growth factor receptor (*EGFR*) mutation to be a negative predictive factor for immunotherapy, with most data explored in classic *EGFR* mutations 19del and L858R[3, 4], while data in patients harboring *EGFR* exon 20 insertion mutation are lacking. High-throughput sequencing such as next-generation sequencing could provide more information for treatment selection.

Here we describe a rare case of a lung adenocarcinoma patient with brain metastases (BM) harboring *EGFR* exon 20 insertion mutation responded to 1st-line PD-1 inhibitor sintilimab plus chemotherapy (pemetrexed and carboplatin), with a continuous partial response both cranial and extra-cranial beyond 1 year.

Case Report

Figure 1 shows the timeline of a 56-year-old man who sought care for dry cough that had been progressively worsening over 4 weeks, he was neurologically asymptomatic and had tobacco use of 1 pack x 20 years. A computed tomographic scan revealed a large mass in the left lower lobe of the lung. Magnetic resonance imaging (MRI) of the head revealed numerous tumor lesions, with mass effect and local edema. A core biopsy specimen of the left lower lobe mass showed lung adenocarcinoma that was positive for cytokeratin 7 (CK7), negative for cytokeratin 20 (CK20), and positive for thyroid transcription

factor 1 (TTF1) on immunoperoxidase staining. The PD-L1 (SP263) testing showed high expression with a tumor proportion score of 90% (figure 2A).

Molecular testing on the biopsied tissue via next-generation sequencing (NGS) revealed an *EGFR* exon 20 in-frame insertion (P772_H773insYNP+H773Y), Microsatellite stability (MS), and high tumor mutational burden (TMB) 10.5 Mut/Mb. Also, alterations in immune-related genes were revealed including *CTNNB1* (Catenin β 1) S37F, and *ARID2* (AT-rich interactive domain-containing protein 2) E1056X, with some variants of unknown significance (figure 2B).

The patient started treatment of chemotherapy (pemetrexed and carboplatin(CBP)) plus PD-1 inhibitor sintilimab in November 2019. After 4 cycles of treatment, the patient achieved a partial response per Response Evaluation Criteria In Solid Tumors, Version 1.1, with a decrease in lung mass, and the brain tumors shrunk continuously. After 6 cycles of treatment, the patient then accepted sintilimab plus pemetrexed every 3 weeks as maintenance therapy, which was well-tolerated without any toxicity and is still ongoing after 15 months since initiation of 1st-line treatment.

Follow-up imaging, by brain MRI, chest, abdominal, pelvic CT, and bone-scan at various time points showed a continuous decrease in the size of both the lung and brain lesions, with no new sites of disease. At a follow-up of 15 months after diagnosis, the patient continued to take pemetrexed plus PD-1 inhibitor, without evidence of progressive disease at last follow-up.

Discussion

EGFR mutations are detected in 20%~50% of lung adenocarcinoma patients, *EGFR* exon 20 insertions are the next most common *EGFR* mutations in NSCLC after classical mutations, accounting for 4-10% of all observed *EGFR* aberration[5, 6]. Most *EGFR* exon 20 insertion mutations predict resistance to clinically achievable levels of tyrosine kinase inhibitors (TKIs) in advanced NSCLC, although there are rare exceptions. Some novel *EGFR* inhibitors have shown encouraging antitumor activity for *EGFR* exon 20 insertions[7], but commercially obtainable effective targeted drugs remain an unmet need in clinical management. Therefore, platinum-based chemotherapy is considered standard treatment for these patients.

This patient harbored *EGFR* exon 20 in-frame insertion (P772_H773insYNP+H773Y). exon 20 H773Y was previously detected combined with exon 20 insertions[6, 8]. Preclinical research indicated that the complex mutations of exon 20 insertion combined with H773Y resist 1st-generation *EGFR*-TKIs[8], while clinical evidence for the effect of 2nd or 3rd generation *EGFR*-TKIs are lacking.

Although ICIs have revolutionized the systemic treatment of patients of NSCLC with *EGFR*^{wild-type (WT)}, the activity and clinical impact in the subgroup of *EGFR* mutation-positive tumors have been lower than in the *EGFR*^{WT} population in large 2nd- and 3rd-line phase III trials and 1st-line trials evaluating the efficacy of ICIs often excluded *EGFR*-mutation-positive patients. Anecdotal evidence suggests that some *EGFR* mutation-positive patients benefit from PD-1/PD-L1 inhibitors[9]. *EGFR* exon 20 mutations demonstrated

a higher response rate and longer survival compared to classic *EGFR* mutations[10]. A case report demonstrated that a heavily pre-treated patient of NSCLC with *EGFR* exon 20 insertion mutation responded to ICIs-based therapy[11]. But the effect of upfront ICIs in lung cancer patients harboring *EGFR* exon 20 insertion mutation is lacking. This patient had high PD-L1 expression, PD-L1 is a positive predictive biomarker of ICIs, which has been prospectively validated and approved by the Food and Drug Administration (FDA), and was also positively associated with outcomes for ICIs in *EGFR* mutant NSCLC[4].

Considering this patient was neurologically asymptomatic, with rare *EGFR* mutations, high PD-L1 expression, and High TMB[12], therefore, 1st-line immunotherapy plus chemotherapy was applied. A durable response was achieved with impressive control in both extra-cranial and cranial tumor lesions.

Brain metastases, associated with poor clinical outcomes, are diagnosed in approximately 20% of NSCLC patients[13]. For asymptomatic BM, upfront systemic chemotherapy could be an option. However, traditional chemotherapy drugs have a limited role in BM management, owing to the presence of efflux pumps[14, 15], and lacking penetration of the blood-brain barrier (BBB). Here is the rational basis for ICIs-based treatment in patients with BM: first, antitumor T cells are activated and home to the brain from extra-cranial sites, second, tumor neo-vessels are leaky to facilitate ICIs penetrating to stimulate tumor-associated T cells. Prospective trials evaluating ICIs efficacy in previously untreated BM are scarce. It was supported by a few studies of anti-PD-1 mono-therapy that ICIs can induce intra-cranial response[16, 17], [18]. Series of retrospective studies provided evidence that intracranial and extra-cranial ICIs efficacy are comparable [16, 19].

Some questions have yet to be resolved regarding how to identify the patients most likely to benefit from ICIs-based therapy, and how to weigh the probability of immunotherapy benefit when concomitant potential positive and negative factors both exist. For this patient, concomitant alterations in immune-related genes were revealed including *CTNNB1* S37F and *ARID2* E1056X. *CTNNB1* S37F is a gain-of-function mutation that could lead to aberrant activation of the WNT/ β -catenin signaling, which is enriched in non-T cell inflamed tumors[20] [21] and has been linked to lack of benefit of immunotherapy in NSCLC[22]. Whereas, *ARID2* E1056X is a loss-of-function mutation. *ARID2*, encoding a PBAF complex subunit, acts as an immunomodulator. *ARID2* mutation is a potential biomarker positively indicating ICIs effectiveness in melanoma patients[23-25]. Considering that biomarkers are often complex and non-binary, and we only see part of the picture since the potential heterogeneity has not been evaluated, therefore, it is overly simplistic to seek predictive power from a single marker. An interconnected network of multiple factors would be the eventual biomarker to form a more complete puzzle.

In conclusion, our case demonstrated that upfront chemotherapy plus PD-1 inhibitor might be an option for some NSCLC patients of BM harboring *EGFR* exon 20 insertion and high PD-L1 expression/high TMB. Additional insights into gene aberrations provide more information. Further study is needed to validate the predictor involved in responders to ICIs-based therapy with *EGFR* mutations.

Declarations

Funding: The authors did not receive any funding for this study.

Conflict of interest: The authors have no conflicts of interest to declare under consideration for publication.

Availability of data and material: All data generated or analyses of this case were included in this published report.

Ethics approval and consent to participate: The patient gave his oral and written informed consent. The case report was approved by the Ethics Committee (Medical Research Ethics Committee of Xuanwu Hospital).

Consent for publication: the patient has signed a consent for publication.

Informed consent Waived by the Institutional review board because of the retrospective nature of this case report.

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Authors' contributions NJY designed the study and wrote the initial draft of the manuscript. GYF assisted in the preparation of the manuscript. All other authors have contributed to review the manuscript. All authors approved the version of the manuscript finally and agree to be accountable for all aspects of the work.

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Figures

Figure 1

Timeline of clinical response. Shown is the timeline of cranial and extra-cranial clinical response of the NSCLC patient with EGFR 20 exon insertion mutant to 1st-line PD-1 inhibitor plus chemotherapy. The evolution of the disease was demonstrated by brain MRI and chest CT at various time points. NGS analyses were performed at the time of diagnosis (October 2019). Sintilimab plus chemotherapy (pemetrexed+CBP) were initially provided for 6 cycles, followed by Sintilimab plus pemetrexed as maintenance therapy.

Figure 2

Histopathologic analyses and Molecular detection by NGS at diagnosis. (A) Histopathologic analyses at diagnosis. (upper left) CT imaging shows the biopsy site (arrowhead) at the left lower lobe mass of the lung. (lower left) Low-power magnification (Original magnification, 10x) shows lung biopsy widely infiltrated by adenocarcinomatous architecture. (upper right) high-power magnification (Original magnification, 40x) shows neoplastic cells with abundant pale eosinophilic cytoplasm and atypical round to oval nuclei. (lower right) 90% of these neoplastic cells express PD-L1. (B) Molecular alterations of lung biopsy by NGS at diagnosis.