CASE REPORT

Mobocertinib and Bevacizumab for Amivantamab-Refractory Lung Cancer With *EGFR* Exon 20 Insertion Mutation: A Case Report

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Received 12 September 2023; revised 20 September 2023; accepted 1 November 2023
Available online - 7 November 2023

ABSTRACT

Amivantamab is the first drug approved in *EGFR* exon 20 insertion-mutated NSCLC. Nevertheless, primary or secondary resistance to amivantamab is a frequent problem in clinical practice. We report a case of a patient with *EGFR* exon 20-mutated NSCLC who had primary resistance to amivantamab but was successfully treated by combining therapy of another *EGFR* exon 20 insertion-specific targeted drug mobocertinib and bevacizumab.

Keyword: NSCLC; EGFR exon 20 insertion; Drug resistance; Anti-angiogenesis; Targeted therapy; Case report

Introduction

EGFR exon 20 insertion (*E*20ins) mutations have been recognized as new targetable driver oncogenic mutations since the approval of two drugs, mobocertinib and amivantamab, in patients with advanced NSCLC.[1,2] Herein, we present a successful treatment of amivantamab-refractory NSCLC with *E*20ins mutation using a combination treatment of mobocertinib and bevacizumab.

Case Presentation

A 51-year-old man with a lung mass was referred to our hospital and diagnosed with having cT2aN2M0 stage IIIA lung adenocarcinoma. The cobas EGFR mutation test detected *E*20ins mutation in the lung tumor tissue. The *E*20ins type was revealed to p.Asp770_Asn771insGly by the direct sequencing test. As the first-line treatment, the patient received concurrent pemetrexed plus cisplatin and thoracic radiation therapy with a total dose of 66 Gy. The patient had stable disease after definite chemoradiotherapy; however, after seven months, the disease progressed, with newly developed multiple lung metastases (Fig. 1*A*). The patient experienced cough and whitish sputum at the time of progression from chemoradiotherapy. As subsequent therapy for advanced *E*20ins-mutated NSCLC, we administered amivantamab to him with the standard dose and schedule. During amivantamab treatment, the patient experienced grade 2 infusion-related hypersensitivity, diarrhea, and skin rash; however, the dose was not reduced until three cycles. After three cycles of amivantamab, the lung metastasis increased markedly, and his cough, productive sputum, and dyspnea worsened (Fig. 1*B*). We performed a gardant360 test using a plasma sample and reconfirmed the existence of *E*20ins mutation. Subsequently, the patient started a combination treatment of mobocertinib 160 mg daily and bevacizumab 15 mg/kg

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Disclosure: Dr. Lee reports receiving consulting fees from Roche, Merck, Yuhan, and Bayer. Dr. Kim declares no conflict of interest.

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Cite this article as: Fu R, Smith J. Mobocertinib and bevacizumab for amivantamab-refractory lung cancer with *EGFR* exon 20 insertion mutation: a case report. *JTO Clin Res Rep*. 2023;4:100600.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2023.100600

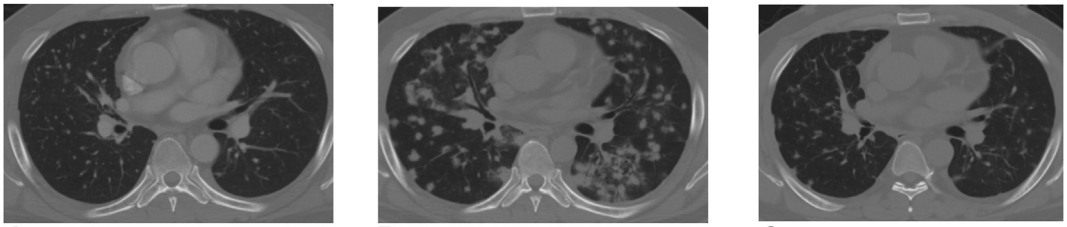

Figure 1. Chest computerized tomography scans during treatment. (*A*) Before amivantamab. (*B*) After third cycle of amivantamab. (*C*) After second cycle of mobocertinib plus bevacizumab.

every 3 weeks. Owing to grade 2 diarrhea and oral mucositis, mobocertinib was temporarily discontinued after one week. Nevertheless, the patient's dyspnea and cough decreased. Mobocertinib was resumed at a daily dose of 80 mg and was well tolerated. After two cycles of mobocertinib and bevacizumab, the lung metastases significantly decreased at 69% of tumor shrinkage by Response Evaluation Criteria in Solid Tumors version 1.1 criteria,[3] and the patient's symptoms much improved (Fig. 1*C*). The patient continued to receive the combination treatment of mobocertinib and bevacizumab with a good tumor response for 4.6 months.

Discussion

To our knowledge, this is the first reported case of *E*20ins-mutated NSCLC with primary resistance to amivantamab that was successfully treated with subsequent treatments. On the basis of the CHRYSALIS phase I trial, 10% of pretreated patients with advanced *E*20ins-mutated NSCLC had primary resistance to amivantamab, similar to the observations in this case.[2] In addition, almost all patients with an initial response to amivantamab invariably experience acquired resistance. Thus, overcoming drug resistance is one of critical issues that must be solved in the use of amivantamab. In this case, the reason why mobocertinib plus bevacizumab could overcome intrinsic resistance to amivantamab remains uncertain. One possible reason may be the difference in drug efficacy. Although no clinical trials have directly compared the efficacies of these two drugs, the different approaches to suppress *E*20ins mutation suggest a potential difference in the effectiveness between the two agents, depending on the mutation types. Nevertheless, this assumption should be evaluated through a randomized clinical trial.

The other possible reason may be the synergistic effect of EGFR and vascular endothelial growth factor (VEGF) blockers. The VEGF receptor (VEGFR) signaling pathway is a main mediator of angiogenesis in tumor cells, which drives rapid cell growth and progression.[4] Preclinical study reported that angiogenesis with VEGFR activation is significantly increased in *EGFR*-mutant cancer cells resistant to EGFR-targeting drugs.[5] On the basis of these preclinical studies, simultaneous suppression of EGFR and VEGFR has been considered as a promising treatment strategy in cancer cells with *EGFR* mutations resistant to EGFR-targeting drugs. Actually, multiple randomized clinical studies evaluating combination treatments with EGFR- and VEGFR-targeting agents have revealed a strong synergistic effect in patients with advanced NSCLC with common *EGFR* mutations (NEJ026, RELAY, and ARTEMIS-CTONG1509). More recent study combining anti–PD-(L)1 and anti-VEGFR inhibitors has also revealed significant survival benefits in patients with advanced NSCLC having *EGFR* mutations who previously treated with EGFR-targeting drugs (IMpower 150).[5] Especially, Zhi et al.[6] reported a case of lung cancer with *EGFR* exon 20 insertion mutation that revealed sustained clinical benefit from the combination of osimertinib plus bevacizumab after the failure to osimertinib. Taken together, these results may support the possibility of a synergistic effect between *E*20in-specific targeted drug and antiangiogenic drug in this patient whose *E*20in-mutated tumor was fully unresponsive to amivantamab.

Conclusions

This case report suggests that a combination treatment of mobocertinib and bevacizumab may be an option to overcome resistance to amivantamab in patients with advanced *E*20ins-mutated NSCLC.

Clinical Practice Points

- Some NSCLC with *EGFR* exon 20 insertion mutations is completely unresponsive to amivantamab.
- A combination treatment of mobocertinib and bevacizumab may be an option to overcome resistance to amivantamab in patients with advanced *E*20ins-mutated NSCLC.

CRediT Authorship Contribution Statement

Youngjoo Lee: Conception and design; Development of methodology; Acquisition of data (e.g., provided

animals, acquired and managed patients, and provided facilities); Analysis and interpretation of data (e.g., statistical analysis, biostatistics, and computational analysis); Writing, review, and/or revision of the manuscript; Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases); Study supervision.

Jaemin Kim: Acquisition of data (e.g., provided animals, acquired and managed patients, and provided facilities); Writing, review, and/or revision of the manuscript; Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases).

Acknowledgments

This study was supported by a National Cancer Center grant (grant number 2210740-2).

Informed Consent

Written consent was obtained from the patient.

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