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CASE REPORT

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Dacomitinib as a retreatment for advanced non-small cell lung cancer patient with an uncommon EGFR mutation

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Abstract

In non-small cell lung cancer (NSCLC), uncommon epidermal growth factor receptor (EGFR) mutations are mutations other than Ex19 deletion and Ex21 L858R, which are common mutations highly sensitive to EGFR-tyrosine kinase inhibitors. Afatinib, a second-generation EGFR-tyrosine kinase inhibitor, has been shown to be effective in patients with uncommon mutations. Dacomitinib, another second-generation EGFR-tyrosine kinase inhibitor, has not previously been shown to be effective in patients with uncommon mutations. Here, we report the efficacy of dacomitinib for uncommon EGFR mutations in a 71-year-old woman diagnosed with metastatic lung adenocarcinoma with uncommon EGFR mutation (Ex18 G719A). Afatinib was administered as the first-line treatment, and a remarkable antitumor effect was observed. However, the tumor grew after 14 months. Pemetrexed plus carboplatin followed by pemetrexed, docetaxel, atezolizumab and S-1 were performed in sequence. Although approximately four years had passed since the start of treatment, her physical condition was good. The patient started dacomitinib as the sixth-line treatment. Lesions were markedly reduced and treatment with dacomitinib was continued for 7.8 months. Dacomitinib is a possible treatment option for NSCLC with uncommon mutations.

KEYWORDS

afatinib, dacomitinib, EGFR-TKI re-administration, non-small cell lung cancer, uncommon EGFR mutation

INTRODUCTION

In non-small cell lung cancer (NSCLC), uncommon epidermal growth factor receptor (*EGFR*) mutations are those other than Ex19 deletion and Ex21 L858R, which are common mutations and are highly sensitive to EGFR-tyrosine kinase inhibitors (TKIs). Uncommon *EGFR* mutations are infrequent, accounting for approximately 10% of total *EGFR* mutations, and are very heterogeneous in patients with NSCLC. Therefore, studies on the biological mechanisms of these mutations are limited. Afatinib is a second-generation EGFR-TKI that has been shown to be effective in NSCLC patients with uncommon mutations.[1] Dacomitinib is another second-generation EGFR-TKI that, like afatinib, is an irreversible inhibitor that shows activity against the pan-ErbB family, with activity against not only ErbB1 (EGFR) but also ErbB2 (HER2) and ErbB4 (HER4). Dacomitinib has been previously reported to improve the survival of patients with NSCLC harboring common *EGFR* mutations.[2] However, dacomitinib has not been shown to be effective in patients with uncommon mutations.

CASE REPORT

A 71-year-old woman was diagnosed with metastatic lung adenocarcinoma (cT4N3M1 stage IV) in March 2016. An uncommon *EGFR* mutation (Ex18 G719A) was detected in

specimens of the primary lesion using polymerase chain reaction (PCR)-based molecular testing. Afatinib was administered as the first-line treatment, and a remarkable antitumor effect was observed. However, tumor growth was observed after 14 months. PCR-based *EGFR* testing of the rebiopsy specimen of the primary lesion revealed the originally detected uncommon *EGFR* mutation. The patient received four cycles of pemetrexed plus carboplatin followed by 16 cycles of pemetrexed as the second-line treatment. Several courses of docetaxel, atezolizumab, and S-1 were subsequently performed in sequence. Before each treatment change, PCR-based *EGFR* testing was performed using tissue of the primary lesion or cell block of the malignant pleural effusion. Ex18 G719X mutation was detected in all samples, except once when no *EGFR* mutation was detected. Although approximately four years had passed since the start of treatment, the patient's physical condition was good. We took another biopsy from the growing primary lesion, and adenocarcinoma with the *EGFR* mutation (Ex18 G719X) was detected. The patient started dacomitinib (45 mg per day) as the sixth-line treatment. Lesions were markedly reduced after the start of dacomitinib (Figures 1 and 2). The treatment caused paronychia, which worsened to grade 2 (Common Terminology Criteria for Adverse Events v5.0). Approximately three months later, the treatment became intolerable and was withdrawn. The drug discontinuation improved paronychia, but there was a slight increase in tumor growth. Dacomitinib was restarted at a reduced dose of 30 mg per day. The lesion shrank again, but significant progression of the primary lesion was then detected by chest CT scan 236 days after the start of treatment (Figure 2). Two cycles of nivolumab were then administered. However, consciousness disorder due to meningitis carcinomatosa appeared. PCR-based *EGFR* testing was performed using cerebrospinal fluid; in addition to G719X in Ex18, E709X mutation was also detected. The patient's general condition deteriorated significantly, which made it difficult to continue treatment, and she died two months after the end of treatment with dacomitinib.

DISCUSSION

First-generation EGFR-TKIs are not effective for NSCLC with uncommon *EGFR* mutations.[3] A multicenter phase II trial reported the efficacy of osimertinib, a third-generation EGFR-TKI, against NSCLC with uncommon *EGFR* mutations other than T790M.[4] The effectiveness of afatinib against tumors with uncommon mutations, except for T790M and Ex20 insertion mutations, has been reported in a combined post-hoc analysis, and better objective response rate and progression-free survival was shown.[1] Recently reported pooled analysis, which assessed the activity of afatinib in 693 patients with uncommon *EGFR* mutation, showed that afatinib is clinically effective.[5] Kobayashi et al. showed that afatinib, as well as dacomitinib, another second-generation EGFR-TKI, was active against Ba/F3 cells with Ex18 G719X mutation in vitro.[6] Furthermore, readministration with afatinib in advanced NSCLC harboring a common mutation but without Ex20 T790M mutation is considered a treatment strategy.[7] We chose to readminister dacomitinib as a late-line treatment after standard chemotherapy for a case of NSCLC with Ex18 G719X mutation that responded to afatinib and we observed a significant therapeutic effect.

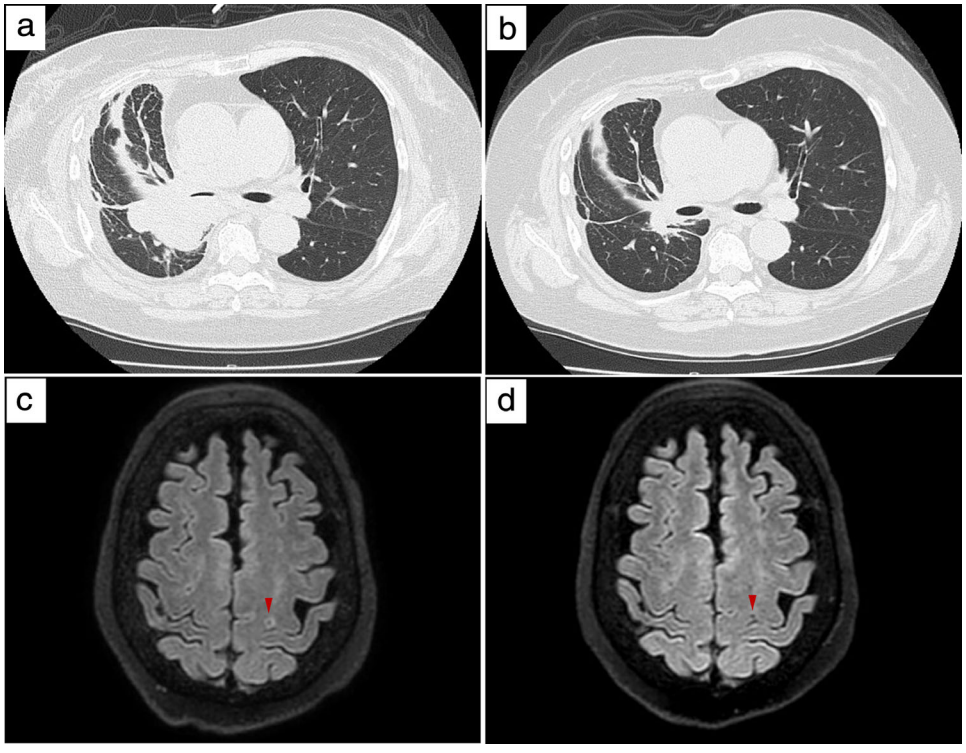

FIGURE 1 Computed tomography (CT) scan showing the primary lesion in the right upper lobe (a) before starting dacomitinib and (b) two months after starting dacomitinib. Magnetic resonance imaging (MRI) showing the largest brain metastasis in the left brain (c) before starting dacomitinib and (d) two months after starting dacomitinib

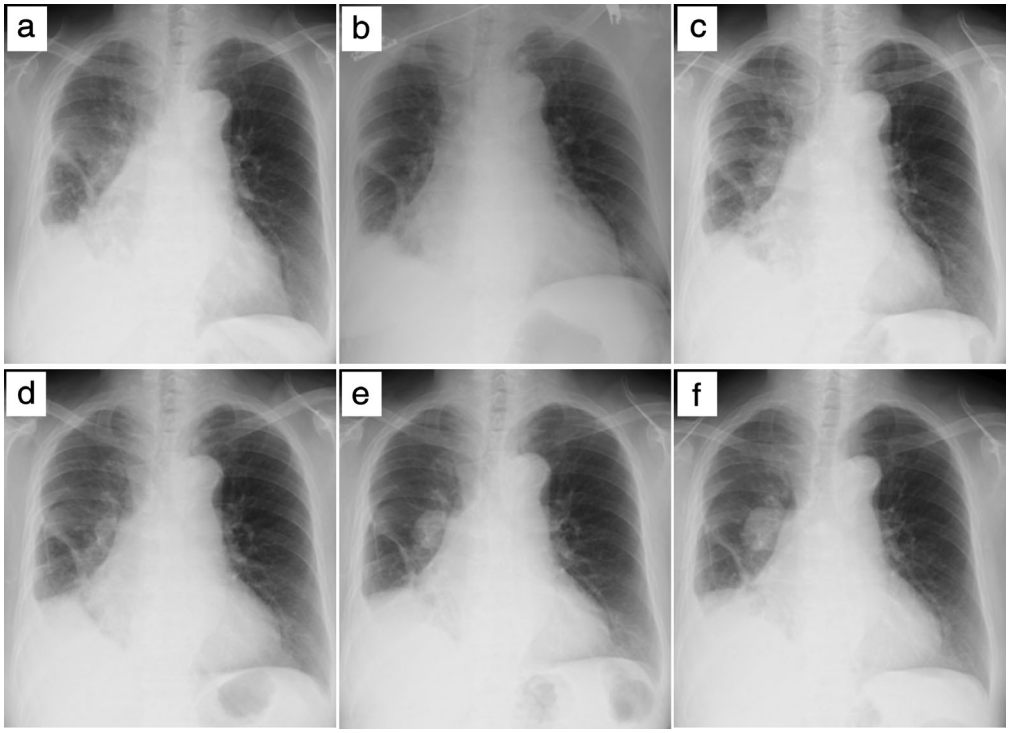

FIGURE 2 Chest X-ray (a) before starting dacomitinib, (b) 71 days after starting dacomitinib (immediately before withdrawal of dacomitinib), (c) 110 days after starting dacomitinib (immediately before restarting dacomitinib), (d) 144 days after starting dacomitinib, (e) 215 days after starting dacomitinib, and (f) 236 days after starting dacomitinib

To our knowledge, this is the first report to show the efficacy of dacomitinib for the treatment of NSCLC with an uncommon *EGFR* mutation. However, there is insufficient knowledge about the activity of dacomitinib against other types of uncommon mutations, even in vitro. In the current case, E709X mutation in Ex18, which had not been previously detected in the patient, was identified by testing of the cerebrospinal fluid after dacomitinib became ineffective, which could be the cause of resistance. The reason that afatinib is effective against NSCLC harboring uncommon *EGFR* mutations is not yet known. Sato et al. recently suggested that ErbB2 participates in EGFR L861Q-driven tumorigenesis and pan-ErbB inhibitors are likely to be effective.[8] Although this report suggested that second-generation EGFR-TKI may be useful for uncommon mutations, cases with uncommon mutations seem to be a heterogeneous population, and future studies should examine the mechanisms underlying individual mutations.

In conclusion, in this study we observed a remarkable effect of dacomitinib for an advanced NSCLC patient with an uncommon *EGFR* mutation. Our findings suggest that dacomitinib may be a treatment option for these patients.

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CONFLICT OF INTEREST

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REFERENCES

1. Yang JC, Sequist LV, Geater SL, Tsai C-M, TSK M, 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;16:830–8.
2. Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18:1454–66.
3. Chiu CH, Yang CT, Shih JY, Huang MS, Su WC, Lai RS, et al. Epidermal growth factor receptor tyrosine kinase inhibitor treatment response in advanced lung adenocarcinomas with G719X/L861Q/S768I mutations. J Thorac Oncol. 2015;10:793–9.
4. Cho JH, Lim AH, An HJ, Hwan Kim K, Uk Park K, Joo Kang E, et al. Osimertinib for patients with non–small-cell lung cancer harboring uncommon EGFR mutations: a multicenter, open-label, phase II trial (KCSG-LU15-09). J Clin Oncol. 2020;38:488–95.
5. Yang JC, Schuler M, Popat S, Miura S, Heeke S, Park K, et al. Afatinib for the treatment of NSCLC harboring uncommon *EGFR* mutations: a database of 693 cases. J Thorac Oncol. 2020;15:803–15.
6. Kobayashi Y, Togashi Y, Yatabe Y, Mizuuchi H, Jangchul P, Kondo C, et al. EGFR exon 18 mutations in lung cancer: molecular predictors of augmented sensitivity to afatinib or neratinib as compared with first- or third-generation TKIs. Clin Cancer Res. 2015;21:5305–13.
7. Oda N, Hotta K, Ninomiya K, Minami D, Ichihara E, Murakami T, et al. A phase II trial of EGFR-TKI readministration with afatinib in

advanced non-small cell lung cancer harboring a sensitive non-T790M EGFR mutation: Okayama lung cancer study group trial 1403. Cancer Chemother Pharmacol. 2018;82:1031–8.
8. Sato H, Offin M, Kubota D, Yu HA, Wilhelm C, Toyooka S, et al. Allele-specific role of ERBB2 in the oncogenic function of EGFR L861Q in EGFR-mutant lung cancers. J Thorac Oncol. 2021;16:113–26.

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