CASE REPORT

Dacomitinib overcomes afatinib-refractory carcinomatous meningitis in a lung cancer patient harbouring EGFR Ex.19 deletion and G724S mutation; a case report

Kei Kunimasa1,4 · Naotoshi Sugimoto2,4 · Motohiro Tamiya1 · Takako Inoue1 · Takahisa Kawamura1 · Ryu Kanzaki3 · Jiro Okami3 · Kazumi Nishino1

Received: 1 May 2022 / Accepted: 27 May 2022 / Published online: 3 June 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract
It has been reported that the efficacy of EGFR-TKI is predicted, not by which exon of the EGFR gene is mutated, but by the structural change in the EGFR protein due to the mutation. Here, we present an EGFR-mutated lung cancer patient with a 13-year history of anticancer treatment, in which EGFR ex.19 deletion (E746_S752 > V) and G724S mutations were detected by liquid biopsy during 12th line afatinib treatment, and switching to dacomitinib showed improvement of carcinomatous meningitis. We choose dacomitinib as 14th line chemotherapy based on ex.19 deletion and G724S mutant EGFR structure and its penetration rate to cerebral fluid, which successfully prolonged her life by 6 months. The optimal EGFR-TKI may be selected by understanding the EGFR compound mutation profile by next generation sequencing and predicting the effect based on the structure. Dacomitinib may be effective choice in afatinib-refractory carcinomatous meningitis harboring G724S mutation. This is the first case report showing that a change to dacomitinib responded to afatinib refractory cancerous meningitis.

Keywords Dacomitinib · Afatinib · EGFR structure · Meningitis · EGFR G724S

Introduction
Dacomitinib is an irreversible, oral small-molecule inhibitor of not only EGFR but also the entire ErbB family, including ErbB2, ErbB3, and ErbB4 of tyrosine kinases [1]. Both dacomitinib and afatinib share the same ErbB family inhibitory activity and are classified as second-generation EGFR-TKIs (tyrosine kinase inhibitors). Afatinib was approved by the FDA in 2013, prior to dacomitinib, which was approved later in 2018. In the meantime, osimertinib, a third-generation EGFR-TKI, was approved in 2015 [2]. Consequently, the position of dacomitinib in EGFR-TKI treatment is currently unclear due to the differences in approval timing [3].

Recently, it has been reported that the efficacy of EGFR-TKI is predicted, not by which exon of the EGFR gene is mutated, but by the structural change in the EGFR protein due to the mutation [4]. In this case report, dacomitinib was remarkably effective against afatinib-refractory carcinomatous meningitis in a patient with a long history of treatment with anticancer drugs, including EGFR-TKIs, as long as 13 years, in which combined mutations of EGFR ex.19 deletion and G724S were detected by next generation sequencing (NGS) analysis of circulating tumor DNA during afatinib resistance. The EGFR-TKI choice was effective based on the EGFR structure-based prediction of EGFR-TKI efficacy.

Case presentation
A 65-year-old woman received chemotherapy and radiotherapy for advanced stage lung adenocarcinoma for more than 12 years. The patient had a smoking history of 20 pack-years. The clinical course is shown in Fig. 1A and B. At the age of 53, she was diagnosed with lung
adenocarcinoma (cT2N0M0) and underwent a right middle lobectomy, but pleural dissemination was detected intraoperatively. The patient received adjuvant chemotherapy with cisplatin (40 mg/m² on day 1 and 8 every 4 weeks) and vinorelbine (25 mg/m² on day 1 and 8 every 4 weeks) for four cycles. The EGFR ex.19 deletion mutation was detected by the PNA-LNA PCR clamp method in the surgically resected specimen. Gefitinib (250 mg/day) was started as first line chemotherapy after adjuvant chemotherapy and effective for about 7 years. Thereafter, other regimens followed (Fig. 1A-C). The reverse transcription PNA-LNA PCR test for EGFR mutation had been performed by analyzing surgical tissue at the initial diagnosis and at the time of resistance to 2nd line afatinib. An EGFR T790M mutation was detected in plasma after 5th line CBDCA plus PEM treatment. NGS analysis of circulating tumor DNA was performed by Foundation One® liquid during the course of 12th line afatinib treatment, and EGFR ex.19 deletion (E746_S752 > V) (variant allele frequency (VAF): 1.5%), G724S (VAF: 2.0%) mutations, and TP53 R213* (VAF: 0.47%) mutation were detected. The T790M mutation was not detected in Foundation One® liquid. The G724S mutation is not covered by RT-PCR base EGFR testing, and the actual time of the occurrence of the mutation is not known. The structure-based prediction of EGFR-TKI efficacy in the combined mutation of EGFR ex.19 deletion and G724S suggested that dacomitinib may have higher anti-tumor efficacy than afatinib [4]. The effects of EGFR-TKIs on EGFR protein with EGFR ex.19 deletion and G724S mutations were compared based on data from in vitro experiments from Source Data Fig. 2 in Ref. [4] (Fig. 2). During the 13th erlotinib plus bevacizumab treatment, the patient complained of headache and dizziness, and enhanced magnetic resonance imaging (MRI) of the head showed signs of carcinomatous meningitis. A spinal fluid puncture also revealed adenocarcinoma cells. After the start of the 14th dacomitinib treatment, her symptoms immediately improved, and the head enhanced MRI showed that the cancerous meningitis had improved (Fig. 3). No steroid was administered at the start of dacomitinib, and only a change to dacomitinib resulted in improvement of symptoms. After the change to dacomitinib, serum CEA level showed a downward trend for nearly 3 months, but then turned sharply upward, and the patient died of worsening cancerous meningitis 6 months after starting dacomitinib (Fig. 1B). After starting systemic chemotherapy, she continued anticancer therapy for about 13 years and 4 months.
Discussion

Structure-based classification of EGFR-TKI showed that dacomitinib had a higher antitumor effect than afatinib in lung adenocarcinoma, harboring the combined mutations of EGFR ex.19 deletion and G724S. Of the 18 EGFR-TKIs, including those under development, dacomitinib seems to have the highest antitumor effect, and there may have been no promising alternative to dacomitinib for afatinib-refractory lesions harboring the complex mutation. With a history of more than 12 years of treatment and no remaining promising options, NGS analysis and the structure-based prediction of EGFR-TKI led to the last promising treatment.

In a study examining the penetration rate of eight EGFR-TKIs (including dacomitinib, afatinib, and osimertinib) to the cerebrospinal fluid (CSF) in mice, dacomitinib showed a high penetration rate comparable to that of osimertinib [5]. Since patients with brain metastases were excluded from the ARCHER1050 trial [1], the evaluation of the effect of dacomitinib on brain metastatic lesions is still unclear. However, in the present case, dacomitinib successfully overcame afatinib-refractory carcinomatous meningitis. Furthermore, the higher sensitivity of the structure of EGFR-combined mutations of the ex.19 deletion and G724S [4] suggested that dacomitinib may have an effect on afatinib-refractory lesions. Although there is a report of response to the addition of afatinib to osimertinib in patients with carcinomatous meningitis harboring G724S mutation who developed during treatment with osimertinib [6], there were no reports of improvement by switching to dacomitinib in afatinib-resistant carcinomatous meningitis with G724S mutation, as far as we could find, and this is the first report of such clinical success.

In the present case, the reverse transcription PCR (RT-PCR) base test for EGFR mutation had been performed by analyzing surgical tissue at the initial diagnosis and at the time of resistance to 2nd line afatinib. An EGFR T790M mutation was detected in plasma after 5th line CBDCA plus PEM treatment, but the T790M mutation was not detected in Foundation One® liquid in the 13th treatment. The G724S mutation is not covered by RT-PCR base EGFR testing, and the actual time of the occurrence of the mutation is not known. However, 1st line gefitinib has been effective for as long as 7 years, and if the G724S mutation exists since the
initial diagnosis, the patient may show early resistance to gefitinib.

TP53 mutation is considered to be a poor factor for the efficacy of EGFR-TKI and prognosis in EGFR-mutated lung cancer patients [7]. In Foundation One® liquid analysis of this case, the variant allele frequency (VAF) of TP53 R213* mutation was 0.47%, which was lower than that of EGFR mutations. It has been reported that EGFR-TKI treatment pressure increases the number of genetic mutations, including TP53 mutation [8]. The long-term response to EGFR-TKI suggests that the TP53 mutation may have occurred late in the clinical course. The additional TP53 mutation may accelerate the spread of the tumor, possibly leading to carcinomatous meningitis.

Conclusion

In the present case, the inference of EGFR structure based on NGS analysis may have led to the selection of the optimal EGFR-TKI. During long-term treatment, the mutation profile changed under treatment pressure. Especially in the use of EGFR-TKIs, it may be important to understand the compound mutations of EGFR and select EGFR-TKIs based on the structure prediction.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by K.K, N.S, M.T, T.I, T.K, R.K, J.O, and K.N. The first draft of the manuscript was written by K.K and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the present case.

Consent for publication Informed consent was obtained from the patient.

Conflict of interest Dr. Kunimasa reports honoraria for lecture from AstraZeneca, Chugai Pharma and Novartis. Dr. Sugimoto reports honoraria for lecture from MSD, Eli Lilly, Chugai Pharma, Taiho Pharmaceutical, Dai-ichi Sankyo and Ono Pharmaceutical. Dr. Tamiya reports grants from Ono Pharmaceutical, Bristol-Myers Squibb, Boehringer Ingelheim and honoraria for lecture from Taiho Pharmaceutical, Eli Lilly, Asahi Kasei Pharmaceutical, MSD, Boehringer Ingelheim, AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb; Dr. Nishino reports a grant from Nippon Boehringer Ingelheim and honoraria for lecture from Chugai Pharma, AstraZeneca, Nippon Boehringer Ingelheim, Eli Lilly Japan, Roche Diagnostics, Novartis, Pfizer Merck and other authors have no conflict of interest.

References

1. Wu YL, Cheng Y, Zhou X et al (2017) 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 18:1454–1466
2. Hsu WH, Yang JC, Mok TS, Loong HH (2018) Overview of current systemic management of EGFR-mutant NSCLC Ann Oncol 29:i3–i9
3. Bergonzini C, Leonetti A, Tiseo M, Giovannetti E, Peters GJ (2020) Is there a role for dacomitinib, a second-generation irreversible inhibitor of the epidermal-growth factor receptor tyrosine kinase, in advanced non-small cell lung cancer? Expert Opin Pharmacother 21:1287–1298
4. Robichaux JP, Le X, Vijayan RSK et al (2021) Structure-based classification predicts drug response in EGFR-mutant NSCLC. Nature 597:732–737
5. Kim M, Larym JK, Mohammad AS et al (2019) Brain Distribution of a Panel of Epidermal Growth Factor Receptor Inhibitors Using Cassette Dosing in Wild-Type and Abcb1/Abcg2-Deficient Mice. Drug Metab Dispos 47:393–404
6. Li Y, Lin Y, Wu J, Ye F (2020) Meningeal metastasis patients with EGFR G724S who develop resistance to osimertinib benefit from the addition of afatinib. Transl Lung Cancer Res 9:2188–2190
7. Aggarwal C, Davis CW, Mick R et al (2018) Influence of TP53 Mutation on Survival in Patients With Advanced EGFR-Mutant Non-Small-Cell Lung Cancer. JCO Precis Oncol 2018
8. Blakely CM, Watkins TBK, Wu W et al (2017) Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers. Nat Genet 49:1693–1704

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.