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Case Report

Successful Dasatinib Treatment of Epidermal Growth Factor Receptor-Mutant Lung Adenocarcinoma and *BCR-ABL1*-Positive Chronic Myeloid Leukemia: A Case Report

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Keywords
Dasatinib · Epidermal growth factor receptor mutation · Lung adenocarcinoma · *BCR-ABL1* · Chronic myeloid leukemia

Abstract
Dasatinib, a second-generation *BCR-ABL1* tyrosine kinase inhibitor (TKI), inhibits multiple kinase pathways and is a promising anti-tumor agent for various solid tumors, including lung cancer. Herein, we report a patient with coexisting epidermal growth factor receptor (*EGFR*)-mutant lung adenocarcinoma and *BCR-ABL1*-positive chronic myeloid leukemia (CML). The patient received afatinib for a postoperative intrapulmonary recurrence of lung adenocarcinoma harboring *EGFR* exon 19 deletion. Tumor reduction was achieved with afatinib; however, dose reduction was required because of grade 2 diarrhea and skin toxicity. The reduced dose maintained a partial response. Thirty-one months after introduction of afatinib, he was diagnosed as having *BCR-ABL1*-positive CML and nilotinib was added to his treatment regimen. However, the combination of nilotinib and afatinib aggravated his diarrhea, prompting discontinuation of afatinib. Because nilotinib does not have sufficient anti-tumor efficacy for CML, dasatinib was substituted for nilotinib. Thirty-five months after introduction of dasatinib, bosutinib was substituted for dasatinib because of uncontrollable pleural effusions. Dasatinib achieved 31- and 35-month progression-free survivals for CML and *EGFR*-mutant lung adenocarcinoma, respectively. Dasatinib is thus a therapeutic option for coexisting *EGFR*-mutant lung adenocarcinoma and *BCR-ABL1*-positive CML when TKI combination therapy is contraindicated by severe adverse events. In our patient, adding nilotinib to afatinib led to severe

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diarrhea. When administering TKI combination therapy, drug-drug interactions should be considered.

Introduction

The prognosis of chronic myeloid leukemia (CML) has been dramatically improved by introduction of *BCR-ABL1* tyrosine kinase inhibitors (TKIs). Dasatinib (DASA), nilotinib (NILO), and bosutinib (BOS), which are second-generation *BCR-ABL1* TKIs, have been approved for first-line treatment of CML in the chronic phase. At 12 months, patients with CML receiving DASA reportedly have a confirmed complete cytogenetic response rate of 77% and an estimated progression-free survival (PFS) rate of 96% [1]. NILO does not inhibit Src family kinases, whereas DASA and BOS potently downregulate these kinases, which include cellular Src kinase (c-Src) [2, 3]. c-Src, a nonreceptor tyrosine kinase, plays a role in regulation of cell growth by cooperating with growth factors and receptor tyrosine kinases, including epidermal growth factor receptor (*EGFR*). c-Src is correlated with cancer progression; thus, inhibitors of c-Src are considered a promising approach to treating cancer [4].

The prognosis of *EGFR*-mutant nonsmall cell lung cancer (NSCLC) has also been improved remarkably by *EGFR* TKIs. In one study, the median PFS for afatinib (AFA), a second-generation *EGFR* TKI, was 11.1 months compared with 6.9 months for conventional chemotherapy [5]. Unlike DASA, which is a multi-kinase inhibitor, AFA displays high selectivity for *EGFR*, *HER2*, and *ErbB4* [3].

However, prolonged survival has led to an increase in the incidence of multiple primary cancers. In the USA, the frequency of multiple primary cancers is reportedly approximately 19.0% [6]. Thus, increasing numbers of patients with multiple primary cancers are being encountered, prompting consideration of combinations of targeted drugs. However, the safety of combined targeted therapies remains unclear, TKI combinations occasionally resulting in severe and life-threatening adverse events (AEs) [7]. We here report a patient who achieved long-term PFS for *EGFR*-mutant lung adenocarcinoma and *BCR-ABL1*-positive CML on DASA.

Case Presentation

A 55-year-old Japanese man was referred to our hospital's department of thoracic surgery for resection of a primary lung adenocarcinoma in the right upper lobe. He was an ex-smoker with a 70 pack-year smoking history. His only significant medical history was hypertension and diabetes mellitus. Whole body computed tomography (CT) with contrast enhancement revealed a 40 × 37 mm diameter tumor in the right upper lobe; no metastases were detected. He underwent right upper lobe resection and mediastinal lymph node dissection in May 2007. On macroscopic examination, the tumor was well circumscribed, the maximum diameter being 38 mm. On microscopic examination, the tumor cells showed anisokaryosis, were arranged in a papillary pattern, and had invaded beyond the elastic layer of the pleura. Lepidic carcinoma was found around the tumor. The pathological diagnosis was adenocarcinoma with mixed subtypes (papillary and lepidic) (Fig. 1a). The cancer was classified as p-stage IB (p-T2N0M0) in accordance with the Union for International Cancer Control 6th edition staging system. On genetic examination, an *EGFR* mutation, L747–S752 deletion of exon 19, was detected using the peptide nucleic acid-locked nucleic acid

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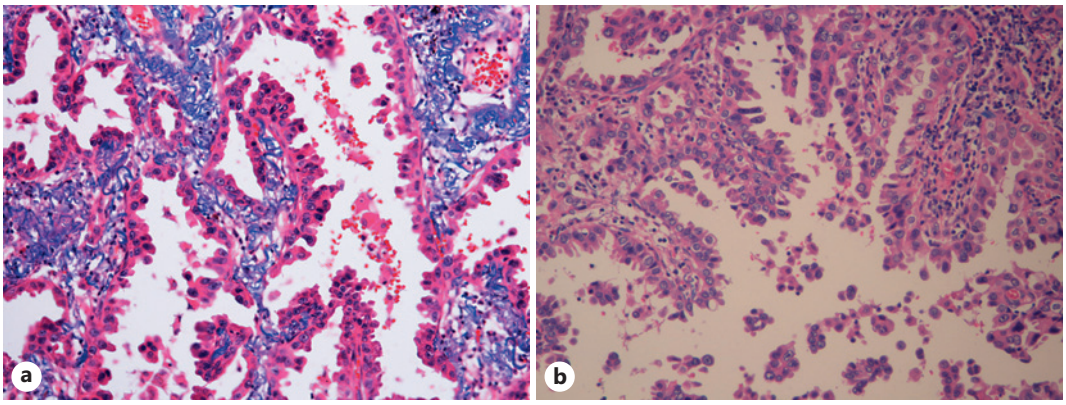

Fig. 1. Pathological findings of lung adenocarcinoma in surgical samples in 2007 (Victoria blue/hematoxylin-eosin stain) (**a**) and 2011 (hematoxylin-eosin stain) (**b**).

polymerase chain reaction clamp method (LSI Medience, Tokyo, Japan). From July 2007, he received four cycles of adjuvant chemotherapy with carboplatin (area under the curve of 5, on day 1) and paclitaxel (50 mg/m^2, on days 1, 8, and 15) every 4 weeks. In May 2010, CT with contrast enhancement revealed a 5 mm diameter nodule in the right middle lobe (RML), which thereafter grew slowly. In August 2011, we performed partial resection of the RML to distinguish between an intrapulmonary recurrence and a new primary lung cancer. Microscopic examination showed the tumor was similar to the previous tumor in the right upper lobe (Fig. 1b). Thus, the pathological diagnosis was recurrence of the previous cancer. Because no other metastases were detected by CT scan, we did not initiate chemotherapy. In November 2013, a new 5 mm diameter nodule was detected in the remaining RML. Because this nodule was slow growing, we suspected an intrapulmonary metastasis of the adenocarcinoma and introduced AFA 40 mg once daily a year later, in November 2014. Three weeks after introduction of AFA, the maximum tumor diameter had decreased from 12 mm to 4 mm. However, 2 months later, we reduced the dose of AFA to 30 mg/day because of grade 2 skin toxicity and diarrhea (assessed in accordance with the Common Terminology Criteria for Adverse Events version 5.0). Fourteen months later, we reduced AFA to 20 mg/day in response to persistent grade 2 skin toxicity. Despite these dose reductions, a partial response (PR) was maintained.

In February 2017, the absolute number of white blood cells in the peripheral blood increased and myelocytes and metamyelocytes were detected. We referred him to the department of hematology. Fluorescent in situ hybridization analysis of peripheral blood cells resulted in detection of *BCR-ABL1* fusion gene. G-band karyotype analysis of bone marrow cells showed 46, XY, t(9;22) (q34;q11.2) in all of the 20 analyzed metaphase cells. Thus, he was diagnosed with *BCR-ABL1*-positive CML. The ratio of *BCR-ABL1* to *ABL1* transcripts on the international scale (*BCR-ABL1 IS*) measured by real-time quantitative reverse transcriptase polymerase chain reaction was 93.1% in peripheral blood. NILO was introduced in June 2017. In July 2017, 1 month after addition of NILO to AFA, he developed grade 2-3 diarrhea. After 2 months of persistent severe diarrhea, he reported grade 3 anorexia. His severe diarrhea and anorexia were associated with a 15 kg weight loss in the 6 months after introduction of NILO. Moreover, laboratory tests in January 2018 showed high concentrations of alkaline phosphatase (864 U/L; grade 2; normal range 120–340 U/L, measured using the Japan Society of Clinical Chemistry's method), gamma glutamyl transferase enzyme (287 U/L; grade 3; normal range 8–60 U/L), and total bilirubin (46.17 μmol/L; grade 2; normal range 2–18 μmol/L). His glucose tolerance was impaired and his fasting blood glucose concentration was high at

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230 mg/dL. Finally, in January 2018, we discontinued AFA but continued him on NILO. Thereafter, *BCR-ABL1 IS* increased progressively from 0.1225% in December 2017, through 0.1335% in February 2018, to 0.1443% in April 2018. Thus, in June 2018, we substituted DASA (40 mg/day) for NILO and gradually increased the dose to 100 mg/day over the following month. Although the nodule's diameter increased from 3 mm in November 2017 (2 months before ceasing AFA) to 8 mm in November 2018 (3.5 months after introducing DASA 100 mg once daily), it decreased to 4 mm in April 2019 (10 months after switching to DASA). PR was maintained thereafter. We therefore concluded that DASA was responsible for the reduction in the diameter of the nodule, which had grown after discontinuation of AFA. A CT scan in November 2018 revealed bilateral pleural effusions, the left effusion being larger. On cytopathologic examination of left-sided pleural fluid having revealed no evidence of malignant cells, we considered the pleural effusions to be an AE of DASA and ceased this drug in January 2021 because of congestive heart failure and increased pleural effusions. We resumed DASA at a lower dose (50 mg/day) in March 2021, 11 weeks after cessation of DASA. However, the pleural effusions increased again. The *BCR-ABL1 IS* decreased to 0.0020% and molecular response 4.5 ($MR^{4.5}$) (*BCR-ABL1 IS* ≤ 0.0032%) was found to have been achieved in November 2020. However, *BCR-ABL1 IS* increased to 1.0093% in April 2021. Given the increasing pleural effusions, we thought the patient had poor tolerability to even the lower dose of DASA and substituted BOS (200 mg/day) for DASA in May 2021. After switching to BOS, pleural effusion has been well controlled. *BCR-ABL1 IS* was decreased and $MR^{4.5}$ was found to have been achieved in May 2022. Thus, DASA and BOS provided 31 months and more than 14 months of PFS for CML, respectively. Up until July 2022, more than 49 months of PFS for lung cancer was achieved after introducing DASA. It is difficult to identify which was responsible for more than 14 months of PFS after substituting BOS for DASA, either DASA's long-lasting effects or BOS's new anti-tumor effects (Fig. 2). The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000527767).

Discussion

To the best of our knowledge, this is the first report of coexisting *EGFR*-mutant lung adenocarcinoma and *BCR-ABL1*-positive CML successfully treated with DASA monotherapy. DASA may be a valid therapeutic option for coexisting *EGFR*-mutant lung adenocarcinoma and *BCR-ABL1*-positive CML when TKI combination therapy is contraindicated by severe AEs. BOS may also be an effective treatment for *EGFR*-mutant lung adenocarcinoma because BOS inhibits Src family kinases, whereas NILO does not. DASA inhibits lung adenocarcinoma cell proliferation by regulating Lin-11/Isl-1/Mec-3 protein kinase 1 activity in vitro and in vivo [8]. Another in vitro study has shown that DASA induces apoptosis of *EGFR*-mutant lung cancer cells [9]. Although the PFS achieved by DASA is inferior to that achieved by standard first-line chemotherapy in patients with advanced NSCLC, in one study one of 30 patients achieved PR and 12 had stable disease (SD) at 12 weeks. Four patients maintained SD for 6 months or longer. The patient with a PR achieved 28 months PFS. Unexpectedly, all 5 patients with long SD or PR had adenocarcinoma with wild-type *EGFR* [10]. Additionally, more than 35 months PFS of lung cancer was achieved with DASA in the present case. These data suggest that a subgroup of patients with NSCLC are extremely sensitive to DASA. The median daily DASA dose of 178 mg in the clinical trial described above was much higher than in our case. Our findings show that standard dosage for chronic-phase CML also has the potential to be effective against lung adenocarcinoma. After substituting BOS for DASA, our patient achieved another 14 months PFS. In the phase 2 trial of DASA, 1 patient achieved

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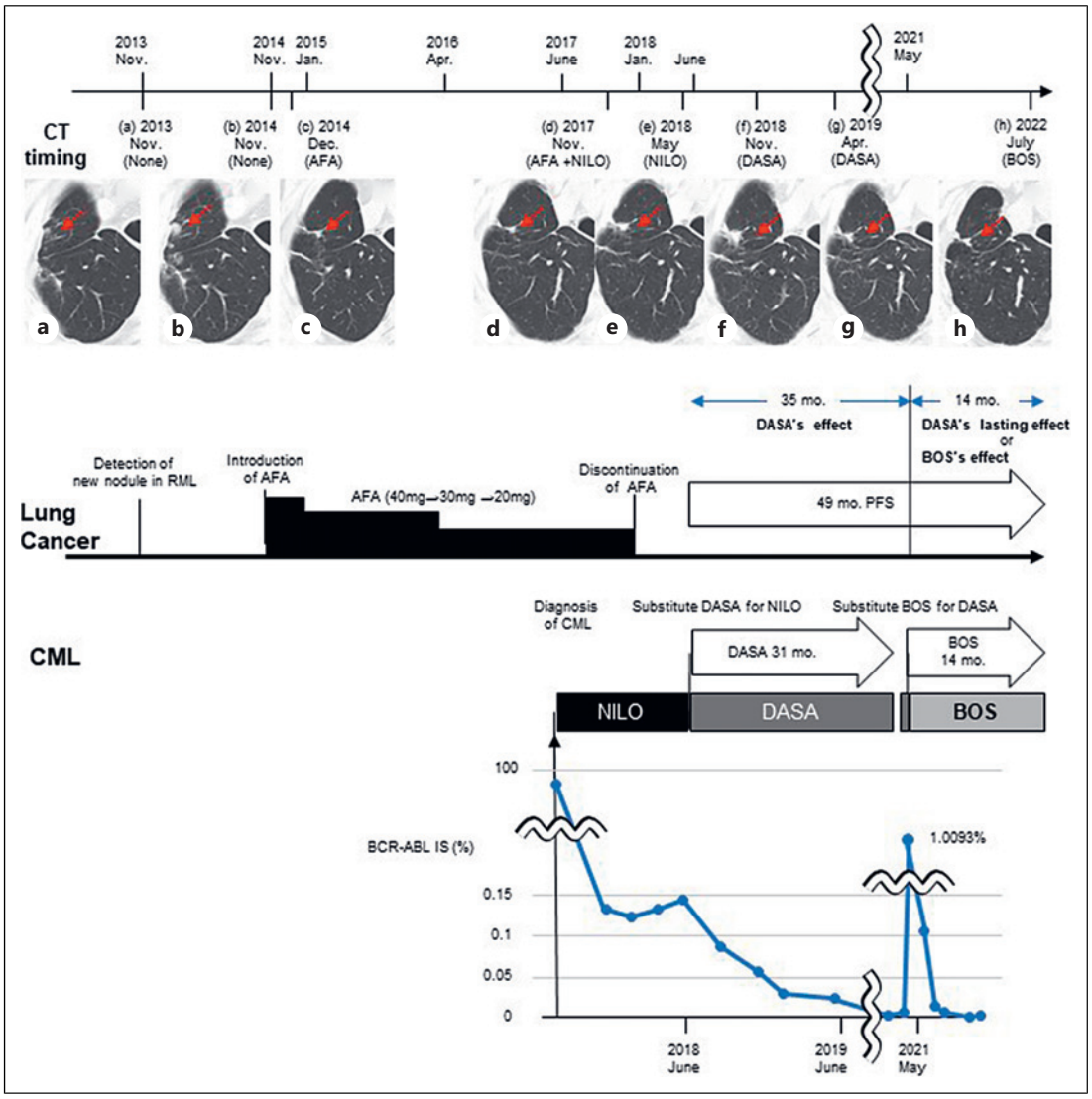

Fig. 2. Clinical course. **a** Changes in tumor size in relation to drug treatment (red arrows) in November 2013, CT image showing there is a new nodule in the RML. **b** November 2014, CT image at time of introduction of AFA. **c** December 2014, CT image 1 month after introduction of AFA. **d** November 2017, CT image 5 months after addition of NILO and 2 months before discontinuation of AFA. **e** May 2018, CT image 4 months after discontinuation of AFA. **f** November 2018, CT image 5 months after substituting DASA for NILO. **g** April 2019, CT image 10 months after substituting DASA for NILO. **h** July 2022, CT image 14 months after substituting BOS for DASA. AFA, afatinib; Apr, April; *BCR-ABL1 IS*, ratio of *BCR-ABL1* to *ABL1* transcripts on the international scale; BOS, bosutinib; CML, chronic myeloid leukemia; DASA, dasatinib; Dec, December; Jan, January; mo, months; NILO, nilotinib; Nov, November; PFS, progression-free survival; RML, right middle lobe.

28 months of PFS, despite only 12 weeks of DASA administration, discontinuation due to malaise, and no other subsequent therapy [10]. Thus, it is difficult to distinguish the long-lasting effects of DASA from the new anti-tumor effects of BOS in extended PFS in our case. In a phase 1 trial of BOS for advanced solid tumors, three of 19 patients with advanced NSCLC had SD for 22–50 weeks [11]. Therefore, BOS may be a valid alternative for treating *EGFR*-mutant adenocarcinoma.

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We noted severe diarrhea as an AE of the combination of NILO and AFA. TKI combinations sometimes result in severe AEs, hindering continuation of combination therapy. Therefore, it is important to consider drug-drug interactions in TKI combination therapy. NILO reportedly inhibits P-glycoprotein and breast cancer resistance protein in vitro and in vivo [12]. Both P-glycoprotein and breast cancer resistance protein are efflux transporters that work against a concentration gradient using the energy from adenosine triphosphate hydrolysis. They transport various substrates, including numerous TKIs [13]. In healthy mice, NILO increases AFA accumulation in plasma and tissues and decreases clearance of AFA [12]. NILO inhibits these two transporters more potently than do DASA and BOS in vitro. DASA and BOS exhibit similar inhibitory potential regarding these two transporters [14]. These data suggest that NILO may be at higher risk of aggravating AEs of another TKI than DASA and BOS.

One limitation of our case report is that we were unable to perform genome profiling of our patient's lung cancer. The surgical sample was obtained 11 years ago and had been discarded, and the ongoing near complete response of our patient's lung cancer prevented us from obtaining new samples. Nearly 40 different kinases have been identified as DASA targets [15]. Thus, gene mutation profiles by next-generation sequencing may enable prediction of biomarkers of DASA efficacy.

In conclusion, DASA may be a valid therapeutic option for coexisting *EGFR*-mutant lung adenocarcinoma and *BCR-ABL1*-positive CML when TKI combination therapy is contraindicated by severe AEs. In our case, severe diarrhea occurred when we added NILO to AFA. When TKI combination therapy is necessary for multiple primary cancers, drug-drug interactions should be considered carefully.

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Statement of Ethics

The patient has given written informed consent for publication of this case report, including the accompanying images. Ethical approval was waivered by the Ethics Committee of Osaka Police Hospital because this is an anonymized case report.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

Akihiro Tsukaguchi, Yoshihiro Kin, and Seigo Minami were involved in treatment of this patient. Hironao Yasuoka made the pathological diagnosis of the tumor. Akihiro Tsukaguchi reviewed previous reports and drafted the manuscript. Seigo Minami was responsible for revision of the manuscript for important intellectual content. All authors have read and approved the final version to be submitted.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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