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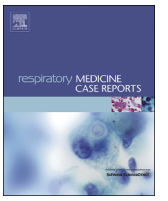

Case Report

Tolerability of sotorasib for *KRAS* positive lung adenocarcinoma patient with pre-existing interstitial pneumonia; A case report

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ABSTRACT

A 74-year-old man was referred to our hospital with an abnormal chest shadow. Computed tomography (CT) revealed a mass in the left upper lobe and interstitial pneumonia (IP). The patient underwent CT-guided needle biopsy and was diagnosed as lung adenocarcinoma with cT2aN1M1a Stage IVA (PUL). The patient was administered 6 cycles of CBDCA + nab-paclitaxel as first-line, 3 cycles of atezolizumab as second-line, and 8 cycles of S-1 as third-line treatment but finally showed tumor progression. Because comprehensive genome profiling test revealed *KRAS* G12C mutation, sotorasib was initiated as fourth-line treatment and showed tumor regression without exacerbation of pre-existing IP.

1. Introduction

KRAS G12C is a target-driven gene detected in approximately 13 % of lung adenocarcinoma [1]. Sotorasib is a recently approved molecularly targeted drug for *KRAS* G12C mutation-positive non-small cell lung cancer (NSCLC) and has shown strong anti-tumor effect on *KRAS* G12C mutant lung cancer [2]. Less frequently, pneumonitis (1.6 %) was observed with all cases reported to be more than grade 3 in severity based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Treatment of lung cancer patients complicated with interstitial pneumonia (IP) is often challenging because of concerning of exacerbation of pre-existing IP triggered by anti-tumor treatment, especially by molecular targeted therapies [3], although *KRAS* mutations are frequently detected as a driver gene abnormality in lung adenocarcinoma with pre-existing IP [4].

In this report, we describe a case of a patient with NSCLC harboring *KRAS* G12C and with pre-existing IP who was successfully treated with sotorasib without an exacerbation of the pre-existing IP.

2. Case presentation

A 74-year-old man was presented to our hospital with abnormal mass on chest X-ray incidentally detected through follow up for his known prostate cancer. The patient had smoking history (35 pack-year). The findings of physical examination were follows; oxy-

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gen saturation with 98 % (ambient air); auscultation of fine crackles in both lower chest fields. The laboratory findings were as follows: CEA, 207 ng/mL; KL-6, 764 U/mL; and SP-D, 32.4 ng/mL. Collagen disease-related autoantibodies were negative. Chest X-ray showed a mass in the left upper lung field. Computed tomography (CT) scan revealed a mass in the left upper lobe invading into the left pleura, a nodule in the right lower lobe, left hilar lymphadenopathy, cystic shadows on both upper lobes, and reticular shadows on both lower lobes (Fig. 1).

A CT-guided needle biopsy for the mass was performed to diagnose as lung adenocarcinoma cT2aN1M1a Stage IVA (PUL). Immunohistochemistry of PD-L1 (clone, 22C3, Agilent) showed negative expression. *EGFR* mutation test (cobas® EGFR Mutation Test, Roche) and immunohistochemistry of *ALK* (clone, 5A4, Nichirei) were negative. Single gene testing was performed instead of next generation sequencing due to lack of sufficient tissue samples. A CT imaging showed emphysema in the upper lobe and diffuse fibrosis in the lower lobe, which was complicated by combined pulmonary fibrosis and emphysema (CPFE). The patient was treated with 6 cycles of CBDCA (AUC5) + nab-paclitaxel (100 mg/m^2) as first-line treatment. After explaining the risk of IP exacerbation to the patient and obtaining his consent, he was treated with 3 cycles of atezolizumab (1200 mg/body) as second-line treatment, and 8 cycles of S-1 (100 mg/day, 1 cycle over 21 days) as third-line treatment but the tumor in the left upper lobe finally showed progression. The clinical symptoms and radiological finding associated with IP did not change during all anti-tumor treatments as mentioned above suggesting the disease behavior of IP could be considered stable.

After these treatments, comprehensive genome profiling test using Foundation One® Liquid CDx showed *KRAS* G12C mutation in his tumor. Sotorasib (960 mg/day) was administered, and CT performed 14 days after the initiation of sotorasib showed tumor regression and the serum level of CEA significantly decreased (Fig. 2). Due to bacterial pneumonia presenting with right upper lobe consolidation and right pleural effusion, the dose was temporarily discontinued and reduced (720 mg/day). Eventually, sotorasib could safely be administered until the disease progression at the 69th day without exacerbation of pre-existing IP.

3. Discussion

Four to fifteen percent of patients with idiopathic pulmonary fibrosis have concomitant lung cancer [3]. However, the treatment of lung cancer complicated with IP is often challenging because the probability of acute exacerbation triggered by anti-tumor treatment could be up to 10–25 % and most clinical trials exclude patients with IP [5].

In the Japanese population, approximately 25 % of IP-associated lung adenocarcinomas have driver gene abnormalities, with 20.4 % having *KRAS* mutations [4]. Therefore, *KRAS* mutant lung cancer with pre-exiting IP is highly likely to be encountered, and it is critical to have an extensive understanding of the potential efficacy and side effects of the treatment options available in such cases. Sotorasib is the first clinically available molecularly targeted drug against *KRAS* G12C mutant lung cancer. *EGFR*-tyrosine kinase inhibitors (TKIs) such as gefitinib are the molecularly targeted drugs for the treatment of *EGFR*-mutation positive NSCLC but have shown potentially fatal adverse events of exacerbation of IP. Previous study reported that pre-existing interstitial lung disease (ILD) was confirmed as a strong risk factor for *EGFR*-TKI-induced ILD [6]. In the CodeBreaK100 study, 2 (1.6 %) of 124 patients with *KRAS*

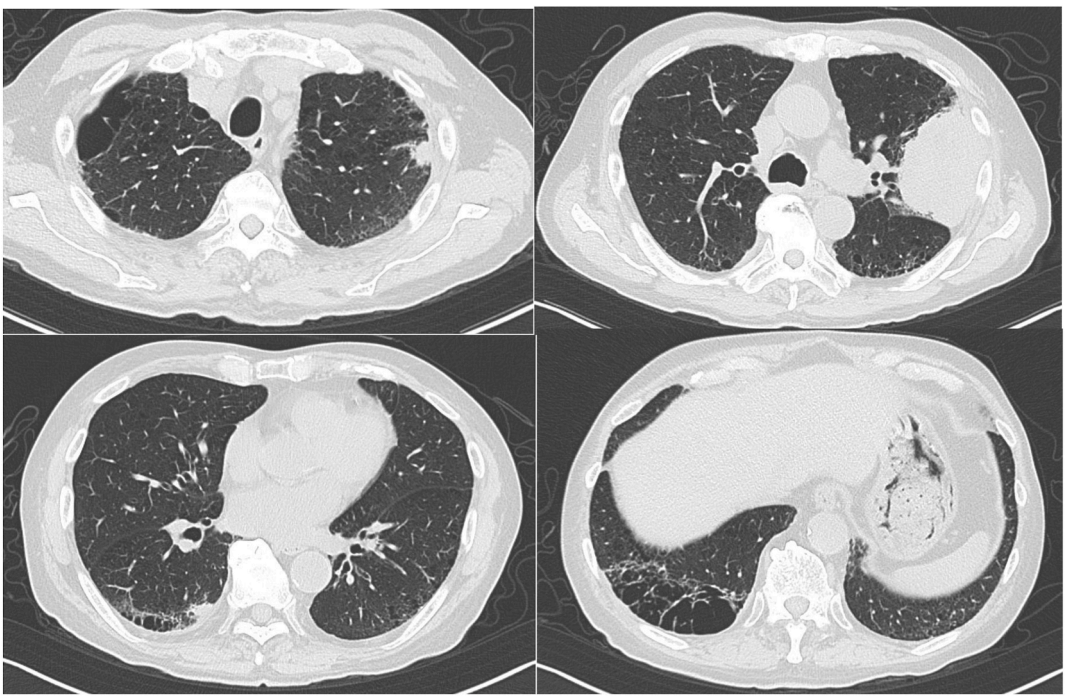

Fig. 1. Chest computed tomography images at the start of sotorasib treatment.

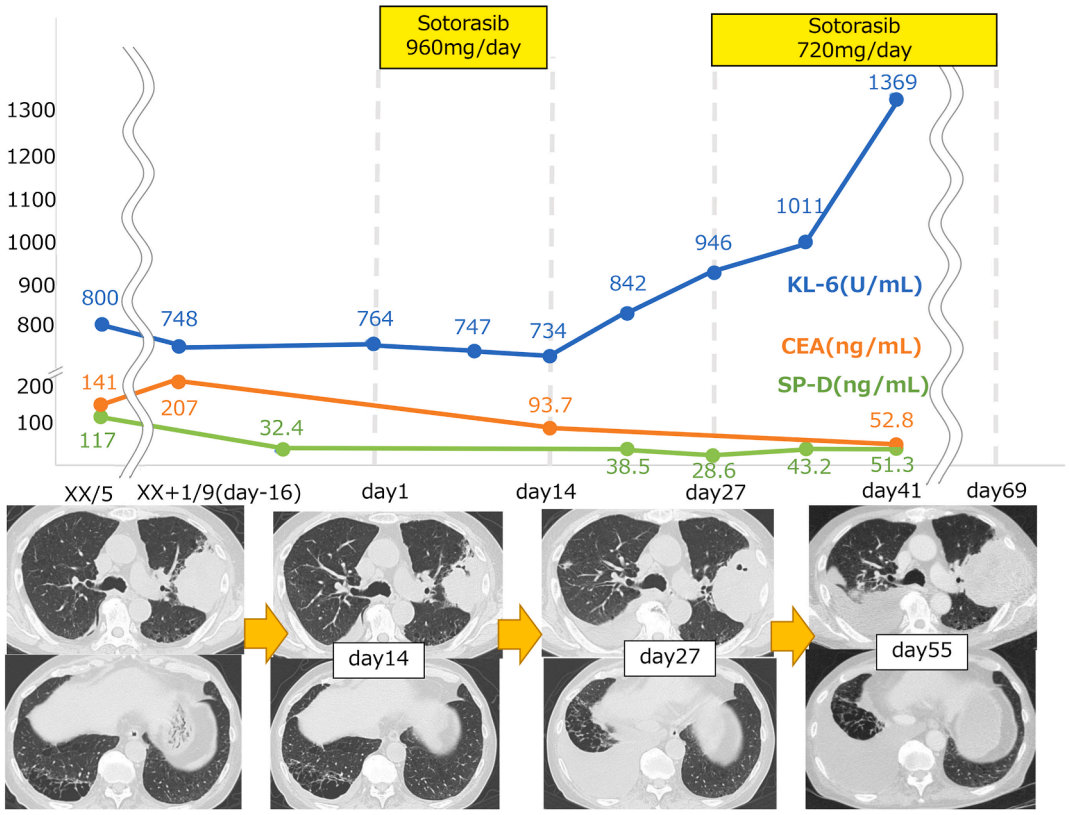

Fig. 2. Clinical course after treatment with sotorasib: computed tomography (CT) imaging after 14 days showed reduced lesions in the left upper lobe; after 27 days, KL-6 increased, but SP-D did not increase, and CT imaging showed no exacerbation of interstitial pneumonia.

G12C mutation-positive lung cancer had lung injury events (Grade 3 and Grade 4) [2]. However, the tolerability of sotrasib for *KRAS*-positive lung cancer with IP has not been reported, and it remains unclear whether this risk factor also applies to molecularly targeted therapy for *KRAS*. Here we report the successful treatment by sotorasib for such a patient without exacerbation of pre-existing IP.

The risk factors for developing ILD in *EGFR*-TKI and chemotherapy are reported to be older age (≧ 55-year-old), poor PS (≧ 2), smoking history, short duration since NSCLC diagnosis (< 6 months), reduced extent of normal lung on CT scan (< 50 %), preexisting ILD, and concurrent cardiac disease [6]. This patient did not meet these risk factors except for older age, smoking history, and pre-existing ILD.

A history of acute exacerbation, elevated KL-6 (≧ 1000 U/ml), and preoperative steroid use have also identified as the risk factors for acute exacerbation of IP associated with surgery in lung cancer [7]. This case did not have any these risk factors.

Furthermore, the patients with “UIP pattern" on high resolution CT had more frequent ILD exacerbations related to cytotoxic chemotherapy and/or surgery than those with “non-UIP pattern” [8]. The frequency of IP exacerbations due to chemotherapy for NSCLC with CPFE is reported to be 9.1 % [9]. While the frequency of acute exacerbations due to chemotherapy for NSCLC with IP is generally reported to be 5.6–32 % [10], the frequency of IP exacerbations due to chemotherapy for NSCLC with CPFE is not high. The present case did not show "UIP pattern” on high-resolution CT and was considered to have stable CPFE based on the CT images, blood tests, and his clinical course. These findings suggest that we could safely treat by sotorasib for *KRAS* G12C mutant lung cancer patient with pre-exiting IP who had few risk factors for developing ILD or acute IP exacerbation due to anti-tumor treatment.

This manuscript has several limitations. First, only one case is presented. Second, we were able to evaluate for only 69 days after initiation of sotorasib. Further case series and analyses for longer observation time are needed to assess the safety and efficacy of sotorasib in patients with *KRAS* G12C mutant lung cancer with pre-existing IP.

4. Conclusion

This case report suggests that sotorasib may contribute to future treatment option for *KRAS* G12C mutant lung cancer with pre-exiting IP.

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Informed consent

We obtained informed consent from the patient described in this manuscript and approval from the Tokyo Medical and Dental University ethics committee.

Declaration of competing interest

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