Clinical Case Report

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Atrial fibrillation was changed into sinus bradycardia in a ROS1-positive advanced lung adenocarcinoma patient who achieved durable response to Crizotinib

A case report and literature review

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Abstract

Rational: The c-ros oncogene 1 receptor tyrosine kinase (ROS1)-rearrangements represent a new and rare genetic subtype of non-small-cell lung cancer. In recent years, the use of crizotinib in ROS1-rearranged lung cancer exhibits significant clinical efficacy. Crizotinib is generally well tolerated and the most frequent adverse events include visual disorders, gastrointestinal disturbances, cardiac, and endocrine abnormalities. From a cardiac perspective, crizotinib is associated with 2 main cardiac effects, QT interval prolongation and bradycardia.

Patient concerns and diagnoses: We reported a case of a 67-year-old man with ROS1-rearranged advanced lung adenocarcinoma.

Interventions: Crizotinib was initiated as first-line treatment, combined with whole brain radiation therapy.

Outcomes: Interestingly, after treatment of crizotinib, the patient suffered a transient QTc interval prolongation and his persistent atrial fibrillation was changed into sinus bradycardia. Only 22 days after crizotinib treatment, the patient's tumor achieved a partial response. So far the patient has taken crizotinib for >19 months with no evidence of disease progression.

Lessons: The present study demonstrates dramatic benefit of crizotinib for patients with ROS1 rearrangement. Besides, we should caution the cardiac effects caused by crizotinb and our case provides evidence that crizotinib may be safe for patients with atrial fibrillation under close monitoring.

Abbreviations: ALK = anaplastic lymphoma kinase, Bpm = beats per minute, CT = computed tomography, CYP3A = cytochrome P450, family 3, subfamily A, ECG = electrocardiogram, EGFR = epidermal growth factor receptor, KRAS = kristen rat sarcoma viral oncogene, MET = mesenchymal epithelial transition, MRI = magnetic resonance imaging, NSCLC = non-small-cell lung cancer, PFS = median progression-free survival, ROS1 = c-ros oncogene 1 receptor tyrosine kinase.

Keywords: atrial fibrillation, cardiotoxicity, crizotinib, lung cancer, ROS1 rearrangement

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide. For certain patients with non-small-cell lung cancer (NSCLC), molecularly targeted therapies have transformed treatment and improved outcomes. The most-studied driver pathways have been the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) pathways. For these 2 genetic subtypes, targeted therapies represent the standard care for the superior efficacy and improved tolerability, as compared with cytotoxic chemotherapy.[1,2] ROS1 rearrangement has been identified as a new target and reported in 1% to 2% of unselected NSCLC. Patients with ROS1 rearrangement have distinct clinical characteristics, including younger age, no or slight smoking history, and histology of adenocarcinoma.[3] Crizotinib is a multitarget tyrosine kinase inhibitor, which is proved safe and effective for ALK-rearranged, mesenchymal epithelial transition (MET)-amplified, and ROS1-rearranged NSCLC patients.[2–4] In clinical practice, common treatment-related adverse events associated with crizotinib are vision disorders, gastrointestinal disturbances, cardiac, and endocrine abnormalities and most of them are grade 1 or 2 in severity.[5] From a cardiac perspective, crizotinib may lead to bradycardia and/or QT interval prolongation, visible on electrocardiogram (ECG).[6] In this case, pretreated ECG showed persistent atrial fibrillation; after the first administration of crizotinib, the patient experienced a transient syncope accompanied with a QTc interval prolongation. The persistent atrial fibrillation turned into sinus bradycardia and the QTc interval returned to normality on the following day.

Editor: Haseeb Zubair.

LL and JW contributed equally to this work.

The authors report no conflicts of interest.

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Medicine (2017) 96:21(e6979)

Received: 3 November 2016 / Received in final form: 7 March 2017 / Accepted: 30 April 2017

http://dx.doi.org/10.1097/MD.0000000000006979

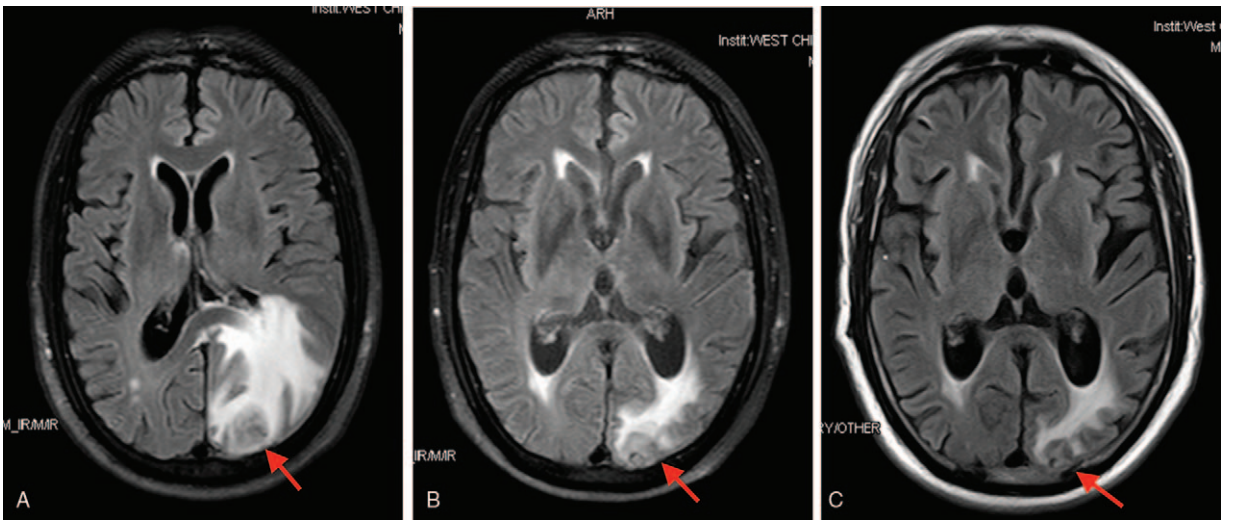

Figure 1. Head magnetic resonance imaging revealed a maximum brain metastasis in the left occipital lobe. (B and C) The maximum brain metastasis showed slight shrinkage after crizotinib and radiation therapy.

2. Case report

In June 2015, a 67-year-old man, a current smoker (90 packs per year), was admitted to our hospital with a complaint of paroxysmal headache, which he had suffered for >20 days. Three months before (March 2015), the patient was diagnosed with hypertension and atrial fibrillation. Hence, he received medications with felodipine, bisoprolol fumarate, and warfarin. But later, he stopped warfarin himself for unknown reason. A physical examination revealed atrial fibrillation and decreased muscle strength of his right leg. His performance status was determined as 3 to 4 points. The brain magnetic resonance imaging (MRI) demonstrated multiple intracranial lesions, and the maximum lesion was in the left occipital lobe accompanied with hemorrhage (Fig. 1A). Computed tomography (CT) scans of chest and abdomen revealed a mass about 4.2×4.0 cm in the right middle lung lobe invading mediastinum and bilateral adrenal metastatic nodules (Fig. 2A). Lung adenocarcinoma was confirmed by bronchoscopy, and ROS1 rearrangement was detected by immunohistochemistry and fluorescent in situ hybridization. No EGFR mutations and ALK-rearrangements were detected in this patient. The patient's clinical stage was determined as T4N3M1b (brain and adrenal gland) (stage IV).

After signing a written informed consent, the patient received crizotinib as first-line therapy at a dosage of 250 mg twice daily from July 9, 2015. Pretreatment baseline of ECG showed atrial fibrillation with a heart rate (HR) of 95 beats per minute (bpm) and QTc interval of 417 ms (Fig. 3A). After the first administration of crizotinib, the patient experienced a transient syncope, which lasted for 3 to 4 minutes. ECG still showed atrial fibrillation with HR of 88 bpm. However, QTc interval prolonged to 454 ms. So he stopped bisoprolol fumarate according to the cardiac physician's suggestion. The second day, ECG showed a sinus bradycardia (59 bpm), and QTc interval returned to 419 ms (Fig. 3B). Although the patient was asymptomatic on the second day, crizotinib was adjusted to 250 mg once every 16 hours for safety consideration. Thereafter, the patient's ECG remained sinus rhythm, and the heart rate fluctuated between 45 to 70 bpm without significant QTc prolongation (Fig. 3C and D). Because the patient had brain metastasis and related symptoms, whole brain radiation therapy (3000 cGy/10f) was started on July 14, 2015. The patient's headache was significantly relieved and his muscle strength improved after treatment. Although brain MRI showed slight tumor regression (Fig. 1B and C), the targeted lesions in the right lung had significantly shrunk (Fig. 2B and C). According to the Response Evaluation Criteria in Solid Tumors criteria, version 1.1, the patient's tumor elicited a partial response to crizotinib treatment. At the time of this report (over 19 months after the

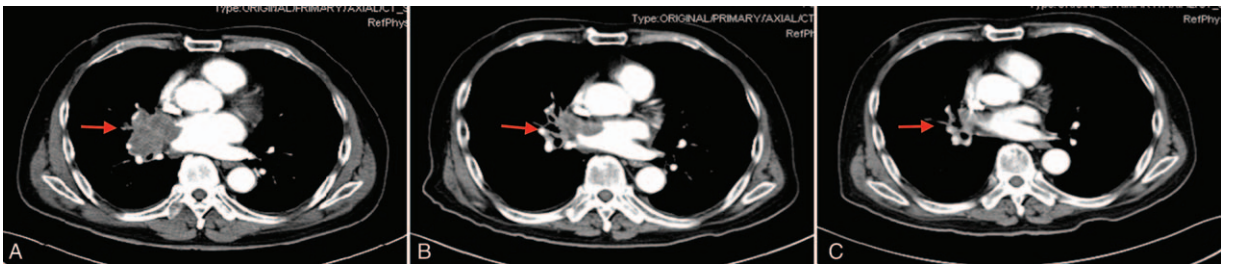

Figure 2. (A) The baseline of chest computed tomography scans revealed a mass in the right middle lung lobe. (B and C) The targeted lesions in the right lung obtained a great cumulative tumor shrinkage after crizotinib therapy.

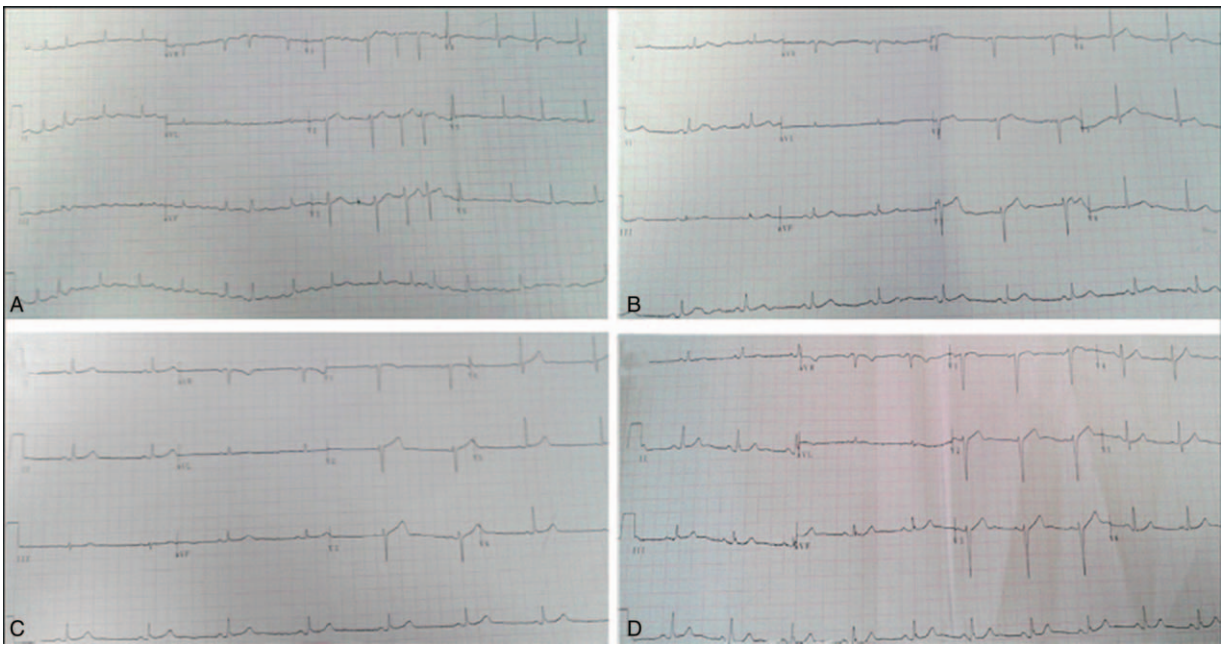

Figure 3. (A) Pretreated baseline electrocardiogram (ECG) showed atrial fibrillation with heart rate of 95 bpm and QTc interval of 417 ms. (B) ECG demonstrated sinus bradycardia (59 bpm) and the QTc interval was 419 ms after continuing the crizotinib to the second day. (C and D) The patient's ECG remained sinus rhythm, and the heart rate fluctuated between 45 and 70 bpm without significant QTc prolongation.

initiation of crizotinib), the patient is still receiving follow-up and treatment with crizotinib orally 250 mg once every 16 hours with no evidence of disease progression.

3. Discussion

Chromosomal rearrangements involving the ROS1 were originally described in glioblastomas. In more recent studies, ROS1-rearrangement was identified as a potential driver pathway in NSCLC cell lines.[3,4] Previous studies have suggested that ROS1-rearrangment is exclusive to other driver mutations in NSCLC.[7,8] However, recent reports have suggested that ROS1-rearrangement occurred in conjunction with other oncogenic driver alterations, including EGFR, Kristen rat sarcoma viral oncogene (KRAS). No coexistence of ROS1- and ALK-rearrangement is reported to date.[9,10] Shaw et al conducted a phase I trial to investigate crizotinib treatment for patients with ROS1-positive NSCLC. Among 50 patients evaluated, crizotinib demonstrated an objective response rate of 72%, and responses to crizotinib were long-lasting, with an estimated median duration of response of 17.6 months. The median time to the first response was 7.9 weeks.[11] In addition, a retrospective trial conducted by Mazie'res et al investigated a European ROS1 cohort of 32 patients who were treated with crizotinib. The reported overall response rate was 80%. Median progression-free survival (PFS) was 9.1 months, and the PFS rate of 1 year was 44%.[12] In our case, as the poor performance status deprived the patient from traditional chemotherapy, he received crizotinib as first-line treatment. Only 22 days after the initiation of crizotinib, the patient's tumor achieved a partial response, accompanied with obvious improvement in symptoms. So far, the patient has taken crizotinib for >19 months, which is longer than most of the patients harboring ROS1-rearranged NSCLC in previous studies.

Crizotinib is well tolerated in patients and the safety profiles in ROS1-positive NSCLC patients are similar with those harboring ALK-rearrangement.[11] Common cardiac disturbances associated with crizotinib in clinical trials include bradycardia and QTc interval prolongation. Sinus bradycardia, a typical grade 1–2 adverse effect, was reported in about 5% of patients receiving crizotinib. Ou et al reported that HR decrease was a common event during crizotinib treatment and 69% of the patients suffered at least 1 episode of sinus bradycardia. The average time of reaching the lowest HR record is 8.6 weeks. Patients with older age, lower pretreatment HR, and longer crizotinib treatment were more likely to experience sinus bradycardia.[5] The pathogenesis of bradycardia under crizotinib is unknown and it may be related to a blockage of certain ion channels. Doherty et al[13] showed that crizotinib inhibits both the sodium (Nav1.5) and L-type calcium (Cav1.2) channels. Ou et al[6] observed that crizotinib lowers the HR without any drop in blood pressure, suggesting that the bradycardic effect of crizotinib is more likely to be chronotropic (which affects the sinoatrial lymph node) or dromotropic (which affects the atrioventricular lymph node) rather than inotropic. It is reported that 1% to 4% patients experienced QT interval prolongation during crizotinib treatment.[5] Crizotinib would be withheld until recovery to grade 1 or to the baseline value when QT interval >500 ms on at least 2 ECGs. Patients should discontinue crizotinib permanently when QT interval >500 ms or prolongation by >60 ms compared to the baseline ECG.[14] In addition, QT interval prolongation will increase the risk to occur torsades de pointes or other severe arrhythmia, which might cause acute short-lasting symptoms for a few seconds or a few minutes, including malaise, faintness, or even fainting.[15]

In the process of treatment, the physician should also consider the potential drug–drug interactions. It is advisable to avoid other bradycardic agents (e.g., β-blockers, nondihydropyridine calcium channel blockers, clonidine, digoxin) when patients

were treated with crizotinib simultaneously.[16] Crizotinib is a moderate strong inhibitor of cytochrome P450, family 3, subfamily A (CYP3A), and also is itself metabolized by CYP3A. So the use of both CYP3A inhibitor and inducer should be considered cautiously. Felodipine is a substrate of CYP3A4, but there is no evidence that indicates that the substrate of CYP3A may have an obvious impact on the use of crizotinib.[14]

In our report, the patient's HR was relatively fast because of persistent atrial fibrillation. HR decrease occurred at the first day of oral crizotinib and the patient experienced a transient syncope accompanied with QTc interval prolonged 37 ms compared to the baseline. Because the ECG was done when the patient was awake, it is difficult to determine whether torsades de pointes or serious arrhythmias has occurred or other unknown reasons that caused the syncope. The patient's atrial fibrillation became sinus bradycardia only after 2 dosage of crizotinib (250 mg) and subsequent ECG remained sinus rhythm. The mechanism is still unclear, although the persistent sinus rhythm may be associated with the influence of crizotinib in the sinoatrial lymph node or atrioventricular lymph node. More data are needed to be collected for analysis and research.

4. Conclusion

The present study demonstrates dramatic benefit of crizotinib for patients with ROS1 rearrangement. Besides, we should caution the cardiac effects caused by crizotinb and our case provides evidence that crizotinib may be safe for patients with atrial fibrillation under close monitoring.

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