Asymptomatic Profound Sinus Bradycardia (Heart Rate ≤45) in Non-small Cell Lung Cancer Patients Treated with Crizotinib

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Abstract: Crizotinib, a dual MET/ALK inhibitor, is now in advanced clinical development for the treatment of anaplastic lymphoma kinase (*ALK*)-rearranged non-small cell lung cancer (NSCLC). We have observed several patients who developed profound but asymptomatic sinus bradycardia (HR ≤45) during the course of crizotinib treatment. Herein, we describe the clinical characteristics of three separate patients enrolled in the A8081001 trial (NCT00585195) who developed asymptomatic profound sinus bradycardia with their accompanying electrocardiogram tracings.

Key Words: Sinus bradycardia, Crizotinib (PF02341066), Pharmacodynamic effect, Non-small cell lung cancer.

(*J Thorac Oncol.* 2011;6: 2135–2137)

Crizotinib is a dual MET/ALK inhibitor that is now in advanced clinical trial in anaplastic lymphoma kinase (*ALK*)-rearranged non-small cell lung cancer (NSCLC) patients. Preliminary results of crizotinib in 82 *ALK*-rearranged NSCLC patients have been published.[1] Crizotinib is generally very well tolerated with mild grade 1 to 2 gastrointestinal disturbances, grade 1 transient peripheral visual disturbances, rare incidences of elevated liver function tests, and even rarer cases of pneumonitis.[1] We also observed that one of the important pharmacodynamic effects of crizotinib in NSCLC patients enrolled in the same trial (NCT00585195) that has not been fully described yet is asymptomatic profound sinus bradycardia (heart rate [HR] ≤45). Herein, we describe the characteristics of three such patients with their accompanying electrocardiograms (ECGs).

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 1556-0864/11/0612-2135

Case 1 is a 32-year-old Chinese female never-smoker with stage IV *ALK*-rearranged NSCLC.[2] She started on crizotinib 250 mg orally twice a day as her fourth-line treatment in early May 2010 with a pretreatment baseline HR of 84 by ECG. Within 2 weeks of starting crizotinib, she developed asymptomatic profound sinus bradycardia (HR ≤45) and persisted throughout her crizotinib treatment (Figure 1). There was no QTc prolongation on ECG, no electrolyte abnormalities, and she had not been on any beta-blockers or calcium channel blockers. Coincidentally, she achieved significant tumor response by computed tomography/positron emission tomography within 2 weeks and achieved partial response by week 4 of crizotinib treatment. She remained asymptomatic with normal blood pressure throughout her entire course of crizotinib treatment without any dose reduction or delay until November 2010 when she developed disease progression.

Case 2 is an 80-year-old Caucasian female with stage IV de novo *MET*-amplified NSCLC with a former 45 pack-year smoking history.[3] Her pretreatment baseline ECG revealed a HR of 71 and a PR interval of 209 milliseconds. She started on crizotinib 250 mg orally twice a day as her second-line treatment in late May 2010 with a day 1 ECG revealing HR of 67 and a PR interval of 230 milliseconds. She achieved rapid symptomatic and radiographic response to crizotinib and a confirmed partial response within 4 weeks. Simultaneously, serial ECGs as required by the protocol revealed sinus bradycardia (HR <55) (HRs in the range of 48–51 and PR intervals of 211–217 milliseconds). She maintained the partial response on crizotinib, and by June 2011, her HRs recorded at follow-up clinic visits revealed profound sinus bradycardia (HR ≤45) (Figure 2). She remained asymptomatic and there were no electrolyte abnormalities and a normal thyroid panel. She had not been on any concurrent beta-blockers or calcium channel blockers. She continued to be on crizotinib at the same dose of 250 mg orally twice a day for the past 14 months without any dose reduction or delay as of her last follow-up on July 20, 2011.

Case 3 is a 50-year-old Mexican male former light smoker (3 pack-year and quit 30 years ago) who was diagnosed with stage IV NSCLC in mid-2006. He started on crizotinib 250 mg orally twice a day as his fourth-line treatment in mid-August 2010 with a pretreatment baseline

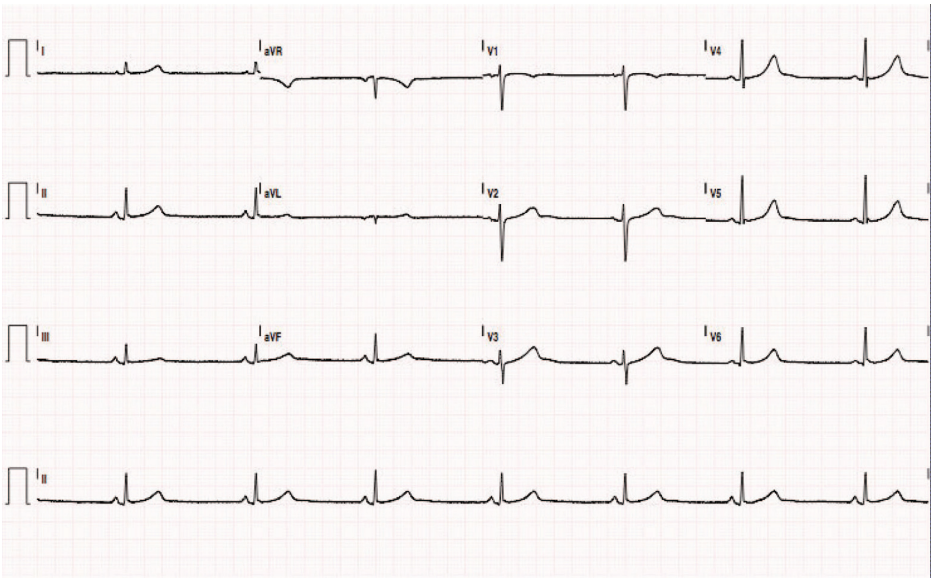

FIGURE 1. A 32-year-old with sinus bradycardia (HR = 43), PR interval of 130 milli-second (ms), and QTc = 439 milliseconds after 2 weeks of crizotinib treatment. Normal range for PR interval = 120–200 milliseconds, normal QTc <470 milliseconds.[6]

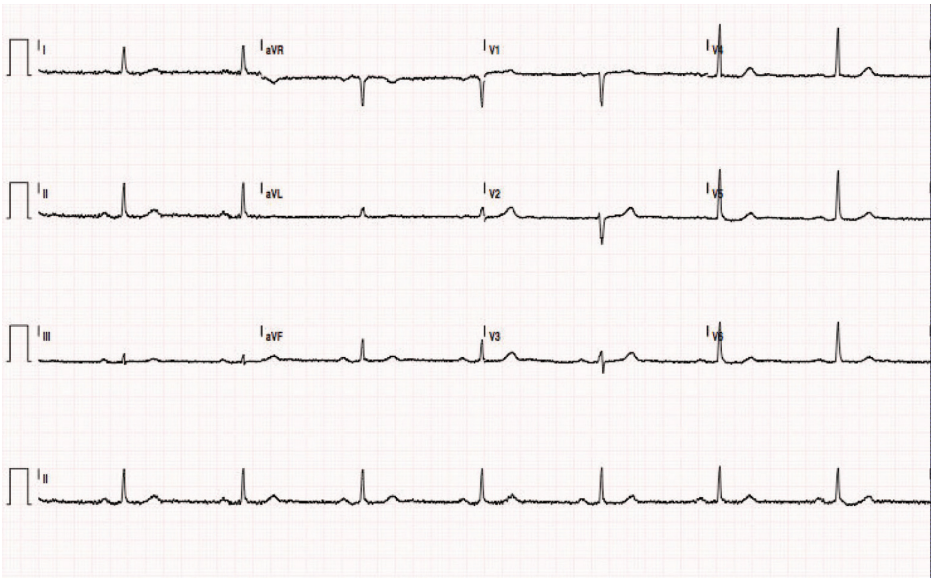

FIGURE 2. A 80-year-old with sinus bradycardia (HR = 44), PR interval of 229 milliseconds (baseline), and QTc of 409 milliseconds after 12 months of crizotinib treatment. Normal range for PR interval = 120–200 milliseconds, normal QTc <470 milliseconds.[6]

HR of 65 by ECG. Serial ECGs on day 1 of crizotinib revealed HRs between 54 and 62. Two weeks later, serial ECGs revealed that he has developed sinus bradycardia (HRs 51–54). By March 2011, he has developed profound sinus bradycardia (HR ≤45) but remained asymptomatic and continued to exercise on a treadmill everyday. ECG recorded his HR to be 39 on a clinic visit in July 2011 (Figure 3). He exercised regularly and his performance status has remained at 0 throughout the 12 months of crizotinib treatment. Again, there were no electrolyte abnormalities with a normal thyroid panel nor was he on any beta-blocker or calcium channel blockers. His blood pressure remained normal throughout his crizotinib treatment. He continued to have confirmed partial response on crizotinib without any dose reduction or delay as of his last follow-up on July 20, 2011.

DISCUSSION

Sinus bradycardia has never been associated with small-molecule receptor tyrosine kinase inhibitors currently being used in cancer therapy.[4] The three patients described here varied in age, gender, ethnicity, smoking status, line of treatment, and time to profound sinus bradycardia. Crizotinib is a small-molecule multitargeted receptor tyrosine kinase inhibitor, and the profound sinus bradycardia observed in some patients is likely due to its dose-dependent pharmacodynamic effects.[5] To date, we have observed eight patients who have developed asymptomatic sinus bradycardia out of 39 *ALK*-rearranged and 1 *MET*-amplified NSCLC patients enrolled in NCT00585195. All eight patients maintained a normal blood pressure throughout their crizotinib treatment.

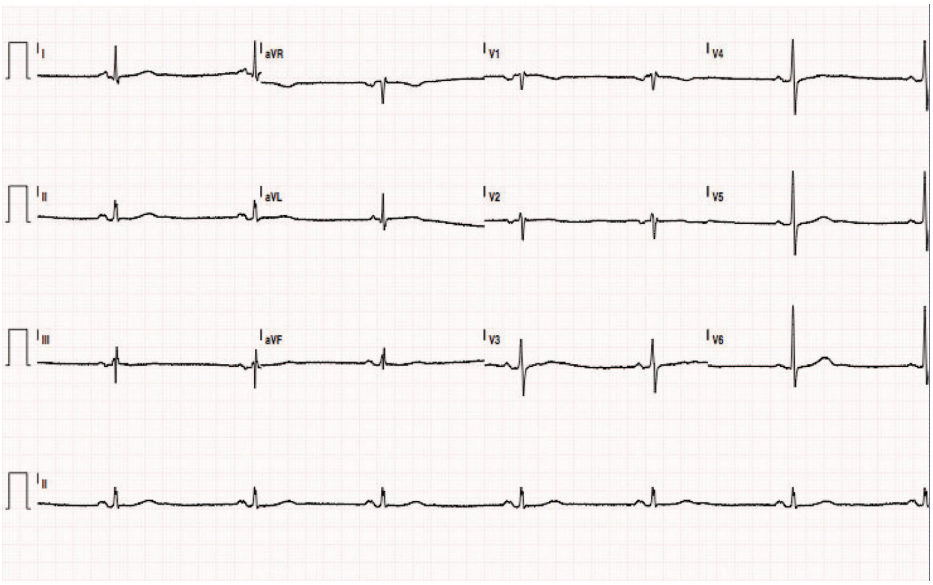

FIGURE 3. A 50-year-old with sinus bradycardia (HR = 39), PR interval of 174 milliseconds, and QTc of 436 milliseconds after 11 months of crizotinib treatment. Normal range for PR interval = 120–200 milliseconds, normal QTc <470 milliseconds.[6]

It will be important to report the incidence of profound sinus bradycardia in the larger cohort of *ALK*-rearranged NSCLC patients enrolled in NCT00585195, the characteristics of these patients, the time to onset of profound sinus bradycardia, and any correlation between profound sinus bradycardia and response. It has been reported that there was an average decrease in HR of 2.5 beats per minute per 100 ng/ml increase in crizotinib concentration without any prolongation of QTc.[5] This dose-dependent and potential dosing-limiting pharmacodynamic effect of crizotinib may be similar to the skin rash observed in epidermal growth factor receptor tyrosine kinase inhibitors. Because the current Common Terminology Criteria Adverse Event only grades sinus bradycardia according to symptoms and whether intervention is required and not by the actual HRs, profound sinus bradycardia as observed in our patients may not be easily noticed within a large clinical trial, especially if they are asymptomatic. Finally, we continued crizotinib on all three patients without dose reduction or delay as they were asymptomatic and benefiting from continuous crizotinib treatment against a deadly disease. We do leave clear instruction for our patients to report any signs of sinus bradycardia such as dizziness or syncope immediately.

Most *ALK*-rearranged NSCLC patients are younger and have never smoked, thus having few if any comorbidities and good performance statuses and can tolerate the profound sinus bradycardia without symptoms. Nevertheless, it is important for the general oncology community to be aware of this pharmacodynamic effect of crizotinib as patients can be on crizotinib for a prolonged period of time, and that a detailed review of symptoms and medications especially beta-blockers and calcium channel blockers such as verapamil and diltiazem is performed before and continuously during crizotinib treatment.

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