Symptomatic Bradycardia Due to Alectinib in a Patient with Advanced Stage of NSCLC

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ABSTRACT

Alectinib is one of the targeted therapies commonly given to patients with advanced non-small cell lung cancer (NSCLC) with mutations in the ALK gene. The most common adverse effects of alectinib are fatigue, constipation, edema, myalgia and anemia. Meanwhile, bradycardia was reported as a very common adverse effect, but generally asymptomatic, unlike the reported patient in this case report. This case report's purpose is to increase awareness of the possibility of adverse effects due to alectinib administration that require immediate intervention in order to improve the quality of life and patient survival, especially in patients with advanced NSCLC.

Keywords**:** *alectinib, bradycardia, NSCLC.*

INTRODUCTION

Lung cancer is the second most common type of cancer in both genders with a 5-year relative survival of 15.7% in the US[1] which are classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[2] Lung adenocarcinoma is one of the NSCLC types.[1] Non-small cell lung cancer with alterations in the ALK gene (ALK positive [ALK+]) is very sensitive to ALK inhibitors, such as alectinib.[3] The administration of alectinib can cause several adverse effects, one of them being bradycardia.[4] Alectinib-related bradycardia is mainly presented as asymptomatic sinus bradycardia,[5] whereas in this case report we elaborate a case of symptomatic bradycardia in ALK+ NSCLC patient treated with alectinib.

CASE ILLUSTRATION

A 57-year-old female patient presented with shortness of breath that had worsened since 10 days prior to the hospital admission in November 2020. The complaint had been getting worse over the past few months, accompanied by dizziness that suddenly occurred and chest heaviness that didn't go away with rest. The patient was diagnosed with ALK+ left lung adenocarcinoma with vertebral metastases in May 2020. The patient has been receiving chemotherapy with alectinib using the reduced dose of 2x300 mg orally (PO) due to recurrent bradycardia in higher doses. The patient's condition was clinically stable for months until bradycardia recurred in November 2020. The patient also took zoledronic acid monthly, mesalazine for Crohn's disease and ursodeoxycholic acid for cholelithiasis which

were both diagnosed several months after the lung cancer. There was diastolic dysfunction from the patient's latest echocardiography in early November 2020.

The patient's vital signs were normal except for a pulse rate of 55 beats per minute (bpm). Physical and laboratory examinations were within normal limits with no signs of peripheral congestion. Chest X-ray examination revealed an image associated with a left lung mass. Initially, the cause of the patient's conditions was thought to be diastolic heart failure. The patient received oxygen supplementation of 3 litres per minute (lpm), anticoagulant and other supportive treatments. Drugs that were routinely consumed were also continued. However, at the first 48 hours of observation, shortness of breath didn't resolve completely. Bradycardia was still ongoing by 45-55 bpm. Re-echocardiography was performed and found grade I diastolic dysfunction with an ejection fraction of 61%.

The patient was diagnosed with symptomatic bradycardia due to alectinib therapy for advanced left lung adenocarcinoma and diastolic heart failure. Alectinib was discontinued. Thereafter, the patient's breath was gradually getting better significantly compared to the admission. The patient's heart rate was also improved, about 55-65 beats per minute. The patient was then discharged after being treated for 6 days.

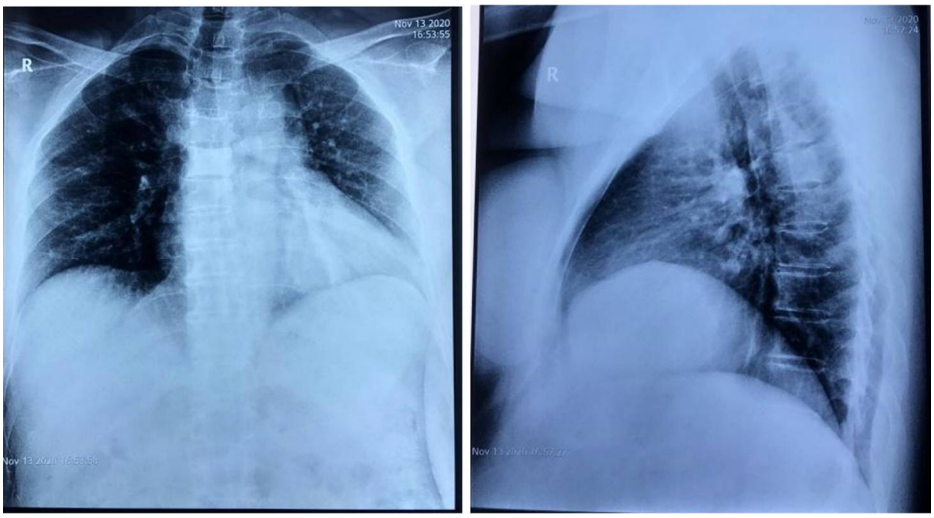

Figure 1. X-ray Imaging of the Patient's Chest.

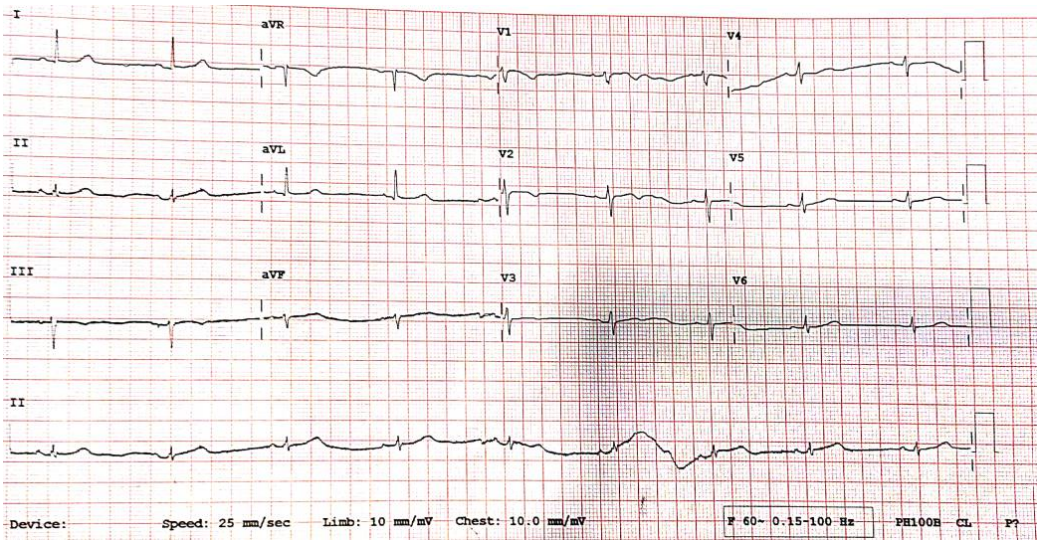

Figure 2. The Patient's ECG on Day 1 of Care.

DISCUSSION

Non-small cell lung cancer patients with distant metastases such as in the brain or bone are generally treated with chemotherapy, targeted therapy, or a combination of both.[1] Alectinib is a targeted therapy for advanced NSCLC with ALK+.[3] The recommended dose of alectinib is 2x600 mg PO. The dose can be reduced to 2x450 mg PO then 2x300 mg PO according to the patient's tolerance and liver function. Alectinib should be discontinued if the patient cannot tolerate the lowest recommended dose.[4]

The most common adverse reactions of alectinib (incidence ≥20%) were fatigue, constipation, edema, myalgia and anemia.[6] Bradycardia was categorized as a very common adverse drug reaction which may occur in ≥1 person out of 10 people.[4] Bradycardia was described as the effect of alectinib on cardiac physiology by a decrease in heart rate of 11-13 beats per minute which is generally asymptomatic, reversible, and majorly presented as sinus bradycardia.[5] Bradycardia occurred in 11% of a total of 405 patients across 3 clinical trials where 18% of patients had heart rates below 50 beats per minute after alectinib administration. There were no cases of symptomatic bradycardia reported.[4] However, according to European Medicines Agency (EMA) and US Food and Drug Administration (FDA), alectinib should be temporarily discontinued if symptomatic bradycardia occurs until the patient's condition improves to asymptomatic bradycardia or until the heart rate is ≥60 beats per minute. Simultaneously, contributing concomitant medication such as anti-hypertensive drugs should be discontinued or have its dose adjusted. Subsequently, alectinib may be resumed at the reduced dose. If life-threatening bradycardia occurs, alectinib should be permanently discontinued if there is no contributing concomitant medications.[4,6] Alectinib can be substituted into drugs of the same class such as ceritinib or brigatinib.[7,8]

In this case report, the patient presented with shortness of breath with sinus bradycardia of 55 bpm with the history of taking the lowest dose of alectinib for about 6 months. There was no significant clinical improvement after the first 48 hours of observation and therapy. Bradycardia was still ongoing. The patient didn't take any medication for diastolic heart failure nor any known drugs that may cause bradycardia, except mesalazine. Out of 4 available case reports, mesalazine-related bradycardia was reported to occur within 24-48 hours after administration of mesalazine either by PO or intravenously (IV).[9-12] The patient didn't have any prior history of bradycardia right after taking mesalazine since September 2020 thus the possibility was disregarded. Another possible cause of bradycardia in this patient is sinoatrial node dysfunction or atrioventricular block which is common in patients with heart failure.[13] However, Holter examination confirmed the sinus bradycardia. Thus, bradycardia was suspected due to alectinib consumption. Alectinib was stopped. Thereafter, the patient's conditions gradually improved.

CONCLUSION

Alectinib is a targeted therapy for NSCLC. One of its adverse effects is bradycardia. Bradycardia is very common and occured in about 11% patients. Although reported cases of bradycardia are mainly asymptomatic, EMA and FDA still warn about the possibilities of symptomatic bradycardia that needs to be treated or even requires immediate treatment during alectinib administration. Rapid identification of adverse effects and appropriate decision making regarding alectinib treatment in patients with advanced NSCLC needs to be encouraged to improve patient's quality of life and survival.

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