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(CASE REPORT)

Second-degree Heart Block in a Patient on Zanubrutinib

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Abstract

Zanubrutinib is a Bruton's tyrosine kinase (BTK) inhibitor recently approved by the Food and Drug Administration for treatment of chronic lymphocytic leukemia (CLL) in January 2023. As a second generation BTK inhibitor, zanubrutinib is more selective for "on-target" BTK and have less cardiac side effects. Although atrial flutter and atrial fibrillation were noted side effects during clinical trials, heart block is not a known side effect. Here we present a case of a patient with CLL on zanubrutinib who presented with a second-degree heart block.

Keywords: CLL; Zanubrutinib; Heart block; Second-degree heart block; BTK inhibitor

1. Introduction

Chronic lymphocytic leukemia (CLL) is a leukemia marked by neoplasm of mature B cells and accumulation of monoclonal B lymphocytes (1,2). It is the most common type of leukemia in adults, accounting for 25-35% of all leukemia diagnoses (1). The mainstay therapy for chronic lymphocytic leukemia (CLL) are Bruton's tyrosine kinase (BTK) inhibitors, with second generation options such as zanubrutinib becoming more popular due to their increased selectivity for B-cell targets (2-4). BTK inhibitors inactivate BTK by binding to cysteine 481 in the ATP-binding site of BTK, located in the kinase domain, creating a covalent and irreversible effect (2,3). This "on target," effect of BTK inhibitors, inactivates the BTK enzyme, and disrupts the BCR signaling, playing a significant role in halting the progression of CLL (3). BTK inhibitors have been shown to have cardiotoxicity effects. The only known reported cardiac toxicity of zanubrutinib, are atrial fibrillation and atrial flutter (2-4); however, there is no literature review of heart block that has been shown with this medication. We report a case of a patient with a history of CLL, taking zanubrutinib three weeks prior to admission, who presented with a second-degree block.

2. Case Presentation

An 87-year-old female with a history of CLL on chemotherapy presented to the emergency department after four days of dizziness, lightheadedness, and weakness. She reported no episodes of syncope or falls. Upon admission her heart rate was between 30 and 40 beats per minute and electrocardiogram (EKG) showed 2:1 heart block (Figure 1a). This heart block was not seen in an EKG taken one year ago (Figure 1b) prior to beginning chemotherapy with Zanubrutinib. She denies any history of cardiac disease and has never had an episode of symptomatic bradycardia. She states that she recently started new chemotherapy with zanubrutinib three weeks prior because her previous medication was not lowering her white blood cell count appropriately. She had completed 40 days of therapy up to the point of her admission per further review. Denied any other medication use such as beta-blockers, calcium-channel blockers, or acetylcholine esterase inhibitors. She complained of palpitations but denied chest pain, shortness of breath, dyspnea on exertion, lower extremity edema, orthopnea. She denied any recent illnesses or international travel. Physical examination findings were remarkable for bradycardia with a sinus rhythm. The patient's heart rate was monitored via telemetry while ambulating.

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Results of this measure did not reveal an appropriate response. Laboratory values were unremarkable with normal thyroid function panel, troponins and brain natriuretic peptide levels. Initial imaging with chest x-ray was unremarkable. Patient was upgraded to ICU, on dopamine drip to maintain her heart rate above 40. Cardiology was consulted and the patient had a pacemaker placed following morning of admission, and symptoms improved.

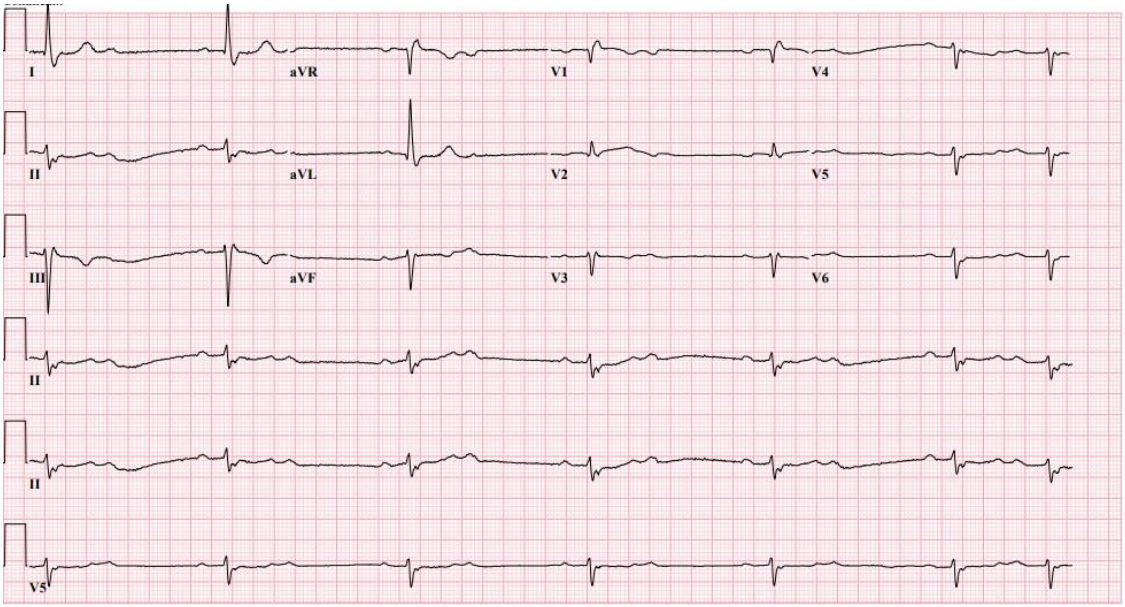

Figure 1a EKG taken on admission demonstrating a 2:1 heart block.

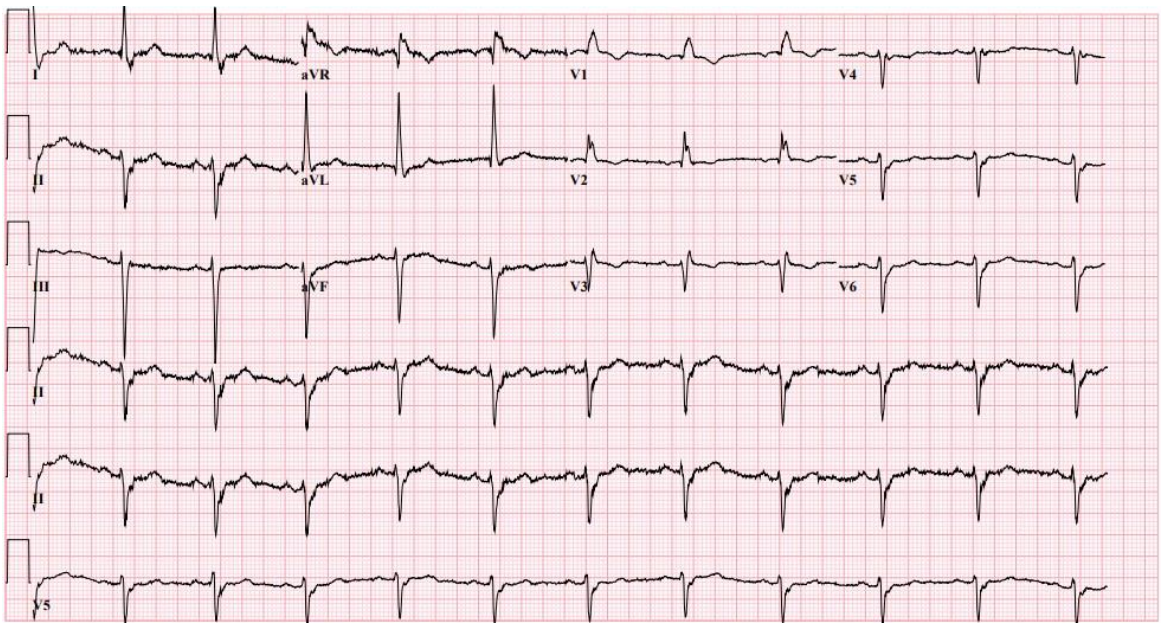

Figure 1b EKG taken one year ago on the same patient that showed sinus tachycardia but did not demonstrate a heart block.

3. Discussion

BTK inhibitors are a first-line option in treating CLL (2). BTK has been found to be an important part of the B-cell receptor signaling pathway that plays a part in B-cell development (3). As such, blocking the pathway plays an important role in treatment of CLL as well as other B-cell lymphomas.

BTK inhibitors are also known to have cardiotoxic effects because these medications are not fully selective for just BTK receptors and can bind to multiple kinases in the cardiac tissue. In fact, both BTK and other kinase, Tec, are found in

cardiac atrial tissue (4). First-generation BTK inhibitors such as ibrutinib is known to cause atrial fibrillation due to the "off-target" kinase activity. One meta-analysis found that the rate of atrial fibrillation in patients taking ibrutinib was 3.3 events per 100 person-years, compared to 0.55 events per 100 person-years in non-treatment groups (5). BTK inhibitors are thought to cause cardiac events by downregulating the Tec tyrosine kinase, an "off-target" kinase affected by these medications.

The benefit of zanubrutinib is that it has greater selectivity for BTK as opposed to "off-target" kinase, therefore it reduces cardiac toxicities (6). And while it may be more selective, zanubrutinb has still been shown to cause arrhythmias. In the ASPEN trial, atrial fibrillation and atrial flutter was found to occur at events per 100 person-months (4). However, there has not been a case reported of heart block in a patient taking zanubrutinib to our knowledge. Our patient had no significant cardiac history and had no heart block a year before this incident. In addition, our patient was not on any other medications that are known to cause heart block and there were no other inciting factors other than the start of a new medication. Therefore, we conclude that zanbrutinib is the most likely cause of our patient's new-onset heart block.

4. Conclusion

Next generation BTK inhibitors, such as zanubrutinib, have been associated with decreased cardiac toxicity. However, heart block has not been reported as a side effect and has not been seen in previous case reports with this medication. Given the onset of symptoms in relation to starting the medication and ruling out other causes, we conclude that the most likely cause of the heart block in this patient was zanubrutinib. We encourage physicians to be vigilant with cardiac side effects of this medication in their patients.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors have no conflicts of interest to declare.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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