Recurrent ventricular fibrillation with different tyrosine kinase inhibitors for chronic myeloid leukemia

Abhisheik Prashar, MBBS, MMed,*† Rahn Ilsar, MBBS, PhD, FRACP,* Fernando Roncolato, MBBS, FRACP,†‡ Andrew Hopkins, MBBS, FRACP*†

From the *Department of Cardiology, St George Hospital, Sydney, Australia, †University of New South Wales, Sydney, Australia, and ‡Department of Haematology, St George Hospital, Sydney, Australia.

Introduction
Imatinib and dasatinib are tyrosine kinase inhibitors (TKIs) used in the management of chronic myeloid leukemia (CML). There is limited data regarding the cardiac toxicity of these drugs and, more specifically, their association with ventricular fibrillation (VF).

Case report
A 33-year-old woman presented to the Emergency Department following an out-of-hospital cardiac arrest. Bystander cardiopulmonary resuscitation was performed. The initial rhythm upon ambulance arrival was VF and she was defibrillated once, with immediate return to sinus rhythm (Figure 1A).

Background medical history included chronic-phase CML for 18 months for which she had been taking imatinib 400 mg daily for 15 months with no other co-medications. A major molecular response had been achieved with imatinib. Most recent BCR-ABL polymerase chain reaction (PCR) showed a rise in the transcript level to 0.22% (previously 0.082%).

Our patient was born and raised in Australia with an Egyptian family background. Family history was unremarkable for sudden cardiac death or cardiac arrhythmia.

Resting electrocardiogram demonstrated sinus rhythm, narrow QRS, normal axis, and normal QTc (Figure 1B). Brain computed tomography was normal. Emergent coronary angiography revealed normal coronary arteries with a normal left ventriculogram.

Transthoracic echocardiogram showed normal left ventricular size and wall thickness with normal systolic function (global longitudinal strain -22%, ejection fraction 65.2%). The atria were normal sized and there were no significant valvular abnormalities. Cardiac magnetic resonance imaging showed normal left ventricular size and systolic function with no late gadolinium enhancement. Inpatient telemetry (limited leads) showed occasional monomorphic closely coupled ventricular ectopic beats with reasonably narrow QRS width.

In response to specific questioning, our patient reported new onset of nonexertional and atypical chest pain since commencing imatinib. At this point, our differential diagnoses included imatinib-related coronary artery vasospasm, imatinib-related ventricular arrhythmias, or a non-drug-related predisposition to sudden cardiac death.

Imatinib was ceased following extensive consultation with hematology. Our patient was discharged home following implantation of a secondary-prophylaxis subcutaneous automated implantable cardioverter-defibrillator (S-ICD) in the expectation of long-term immunosuppression from an active hematological malignancy and its treatment, as well as potential future need for indwelling vascular access.

Key teaching points
- Individual tyrosine kinase inhibitors have different molecular targets for their therapeutic effect, and such differences in action explain their distinct and unique cardiac toxicity profile.
- Ventricular fibrillation may occur as an adverse effect of tyrosine kinase inhibitors such as imatinib and dasatinib that directly inhibit the adenosine triphosphate-binding action of the ABL kinase enzyme.
- Asciminib binds to a different domain of the ABL kinase enzyme and this may result in its reduced ventricular arrhythmia profile.

Keywords: Subcutaneous implantable cardioverter-defibrillator; Sudden cardiac death; Tyrosine kinase inhibitors; Ventricular fibrillation

Heart Rhythm Case Reports 2020;6:770–773

Address reprint requests and correspondence: Dr Abhisheik Prashar, Department of Cardiology, St George Hospital, Sydney NSW Australia 2217. E-mail address: a.prashar@unsw.edu.au.

This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Routine hematology follow-up several weeks later post TKI cessation identified new thrombocytosis. Hydroxyurea 1 g twice a day was commenced owing to rapid rise in her platelet count but did not achieve adequate response. Table 1 demonstrates increasing BCR-ABL PCR transcripts and rising platelet counts over time. Imatinib was recommenced at 400 mg daily and a 30-day event monitor was fitted looking for premature ventricular contractions (PVCs) or ST-segment changes prior to any potential arrhythmia recurrence.

Table 1  Platelet count, BCR-ABL polymerase chain reaction percentage, and QTc interval over time

| Date   | Platelet count (normal reference range: 150–450 × 10^9/L) | Event                                      | BCR-ABL PCR | QTc interval (ms) |
|--------|----------------------------------------------------------|--------------------------------------------|--------------|-------------------|
| 3/18/18| 256                                                      | Imatinib commenced                         | 17%          | 440               |
| 5/25/18| 240                                                      |                                            | 0.082%       |                   |
| 1/21/19| 287                                                      |                                            |              |                   |
| 6/17/19| 381                                                      | VF arrest                                  | 2.5%         | 452               |
| 6/29/19| 1300                                                     | Off imatinib for 2 weeks                   |              |                   |
| 7/25/19| 1889                                                     | Hydroxyurea commenced                      |              |                   |
| 7/30/19| 2118                                                     | Thrombocytopenesis commenced               |              |                   |
| 8/1/19 | 2118                                                     |                                            |              |                   |
| 8/7/19 | 610                                                      | Dasatinib commenced                        |              |                   |
| 8/18/19| 569                                                      |                                            |              |                   |
| 8/21/19| 413                                                      | VF arrest                                  |              |                   |
| 10/16/19| 745                                               | Asccinib commenced                         |              |                   |
| 1/28/20| 212                                                      |                                            | 0.0066%      | 432               |

PCR = polymerase chain reaction; VF = ventricular fibrillation.
Thrombocytopenia was introduced for extreme thrombocytosis, with good effect (Table 1). Bone marrow biopsy showed that CML remained in the chronic phase. Repeat mutation analysis identified the 1348G>A E450K mutation at 70%, which was resistant to imatinib. Therapy was then changed to dasatinib 100 mg nightly and cardiac rhythm continued to be monitored through the event monitor. Routine S-ICD interrogation at this point was unremarkable and the patient remained asymptomatic.

Our patient re-presented to hospital 11 days post commencement of dasatinib with a syncopal episode without injury at home that was followed by a witnessed S-ICD discharge and prompt resumption of consciousness. She confessed to feeling nonspecifically unwell in the moments prior to her collapse and triggered her event monitor appropriately. S-ICD interrogation showed an episode of sinus rhythm with occasional monomorphic PVCs culminating in R-on-T phenomenon disintegrating into VF (Figure 2). An appropriate shock (81 J) restored sinus rhythm. Interrogation of the event monitor’s patient-triggered event showed sinus rhythm with occasional monomorphic PVCs and no change to ST segments (Figure 3). Repeat transthoracic echocardiogram showed no interval changes, documenting a normal heart.

Dasatinib was stopped following consultation with hematology. Following extensive discussions with the patient, a consensus decision was made not to pursue bone marrow transplantation and to trial an alternative non-TKI-based drug, asciminib 40 mg twice a day. In contrast to the adenosine triphosphate–binding action of TKIs such as imatinib and dasatinib, asciminib binds to a distinct allosteric site on the SH1 domain of the tyrosine kinase enzyme and hence has a different mechanism of action. No further sustained ventricular arrhythmias or S-ICD therapy has occurred in more than 6 months since commencement of asciminib. Major molecular response has once again been achieved (BCR-ABL PCR 0.0066%). The patient remains clinically well and is regularly reviewed in hematology and cardiology follow-up.

Discussion

TKIs have revolutionized the management of hematological malignancies, with a significant benefit in CML.1 Our patient was initially commenced on imatinib with good effect but suffered an aborted sudden cardiac death, which raised the possibility of cardiac toxicity from TKI. Our observations may suggest that as individual TKIs have different molecular targets for their therapeutic effect, so may these differences in action potentially explain distinct cardiac toxicity profiles.1,2

Heart failure and left ventricular dysfunction has been reported to occur in 0.5%–1.5% of patients across all trials and retrospective studies of imatinib.1 The proposed mechanism of this side effect is drug-mediated disruption of mitochondrial membrane potential with reduction in cell viability as a consequence of BCR-ABL inhibition.1,3 Our patient’s presentations occurred in the absence of clinical heart failure or of left ventricular systolic or diastolic dysfunction, making drug-related myocardial toxicity less likely.

TKI use has been associated with coronary artery spasm as well as acceleration of coronary and peripheral vascular disease.1,3 Coronary angiography confirmed normal coronary arteries in our patient, which excluded epicardial vessel disease (but not vasospasm) as a driver of ischemia-triggered ventricular arrhythmia. Although drug-provoked coronary artery spasm was raised by the history of new atypical chest pain, the absence of ST-segment changes prior to increased PVC activity and subsequent VF makes this explanation less likely as well.

TKIs have been implicated in polymorphic ventricular tachycardia by enhancing automaticity through increased early and late afterdepolarizations.4,5 Clinical and trial data illustrate that new arrhythmias occurred in ~11% of patients during dasatinib use while QTc prolongation >500 ms was seen in 2% of patients.4,5 Case report data have shown an association between dasatinib and a high burden of PVCs without VF that responded well to cessation of the drug.6 The QTc interval in our case has consistently been normal and there has been no evidence of early repolarization to
suggest an inherited channelopathy as a cause for our patient’s VF. The appearance of isolated PVCs prior to arrest does raise the possibility that direct TKI arrhythmogenic effect may underpin our patient’s presentations. Importantly, the lack of arrhythmia recurrence on asciminib demands explanation.

Hematological malignancy treatment resistance necessitated changing imatinib to dasatinib in our patient. Dasatinib itself is a multitargeted TKI that has 325 times greater activity against BCR-ABL and so is more potent than imatinib. Asciminib, however, does not exert its therapeutic effect by direct ABL kinase inhibition, which gives rise to the hypothesis that the arrhythmias are not due to TKI class effect but rather are the product of reduction in ABL kinase function.

Conclusion
Our case describes recurrent PVC-mediated VF on imatinib and dasatinib but not on asciminib, raising direct ABL kinase inhibition, and not a TKI class action, as underlying arrhythmogenic cause. To the best of our knowledge, our case represents the first in the literature suggesting an association of VF with both imatinib and dasatinib and proposes that asciminib may be a safer choice from a cardiac arrhythmia toxicity viewpoint.

References
1. Medeiros BC, Possick J, Fradley M. Cardiovascular, pulmonary, and metabolic toxicities complicating tyrosine kinase inhibitor therapy in chronic myeloid leukemia: Strategies for monitoring, detecting, and managing. Blood Rev 2018;32:289–299.
2. Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarisation (QT interval). Drug Saf 2013;36:295–316.
3. Fiets RB, Staal AHJ, Cramer GE, Blijlevens NMA. Coronary artery spasms due to tyrosine kinase inhibitors used in chronic myeloid leukemia. Neth J Med 2018;76:330–335.
4. Veer M, Chaturvedi A, Badlani J, Poormima I, Thosani A. Brutinib and polymorphic ventricular tachycardia: a potential association? J Am Coll Cardiol 2019;73:2927.
5. Tomsányi J, Nényei Z, Mátra L, Bozsik B. Brutinib, an approved tyrosine kinase inhibitor as a potential cause of recurrent polymorphic ventricular tachycardia. JACC Clin Electrophysiol 2016;2:847–849.
6. Spechbach H, Morel P, Lorenzini KJ, et al. Reversible ventricular arrhythmia induced by dasatinib. Clin Case Rep 2013;1:20–25.
7. Killu AM, Stevenson WG. Ventricular tachycardia in the absence of structural heart disease. Heart 2019;105:645–656.
8. Xu Z, Cang S, Yang T, Liu D. Cardiotoxicity of tyrosine kinase inhibitors in chronic myelogenous leukemia therapy. Hematol Rev 2009;1:e4.