# Cardiovascular event in chronic myeloid leukaemia treated with tyrosine kinase inhibitor: a case report

**YL Boo *,** MD, MRCP(UK), **Christopher CK Liam,** MRCP(UK), **SY Lim,** MD, MRCP(UK), **ML Look,** MRCP(UK)

*Department of Internal Medicine, Hospital Sultanah Nora Ismail, Batu Pahat, Johor, Malaysia*

* Corresponding author: coolrontin@gmail.com

Hong Kong Med J 2019;25:74–5
https://doi.org/10.12809/hkmj176972

## Case report

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm arising from a pluripotent haematopoietic stem cell. It is associated with an oncogenic fusion gene BCR-ABL, encoding a protein with tyrosine kinase activity.[1] The emergence of tyrosine kinase inhibitors (TKIs) such as imatinib, nilotinib, dasatinib, and ponatinib has revolutionised the treatment and improved overall survival of patients with CML. Pericardial and pleural effusion, pulmonary oedema, left ventricular failure, arrhythmia, and coronary heart disease have rarely been reported in clinical trials with nilotinib.[2] We report a case of acute coronary syndrome in a young woman treated with nilotinib.

A 33-year-old woman presented to Hospital Sultanah Nora Ismail, Johor, Malaysia in February 2017 with first-episode sudden-onset, left-sided chest pain that lasted more than 30 minutes and was associated with nausea, vomiting, palpitations, and profuse sweating. She had been diagnosed with CML 2 years previously and had initially received imatinib with low Sokal score. Her BCR-ABL1 fusion transcript was more than 0.1% after 1 year of treatment, and thus, her treatment was changed to nilotinib 400 mg twice daily, as a second-line TKI. Tyrosine kinase domain mutation analysis was not performed due to lack of resources. She was compliant with medication and showed a good response with her BCR-ABL1 transcript dropping to less than 0.1% after 3 months of therapy. She had no other significant medical or family history. On arrival, she was haemodynamically stable and physical examination was normal. Her initial blood investigations showed normal haemoglobin level (13.6 g/dL), white cell count ($8.3 \times 10^9$/L), platelet count ($240 \times 10^9$/L), kidney, and liver function. Her initial electrocardiogram showed T wave inversion over V2 to V6 with a Q wave in lead III. Subsequent electrocardiograms showed evolving ischaemic changes with ST depression over V2 to V6. Her initial creatine kinase was normal (50 U/L) with negative troponin I, but rose to 950 U/L within 24 hours. Her total cholesterol was 4.2 mmol/L, low-density lipoprotein 1.6 mmol/L, and high-density lipoprotein 0.6 mmol/L. Echocardiography showed normal ejection fraction (55%) with a dilated left atrium and left ventricle. She was diagnosed with non–ST elevation myocardial infarction and started on anticoagulation and dual antiplatelet therapy. Urgent angiography showed 95% distal right coronary artery stenosis with successful angioplasty and stenting (Fig). She was discharged from the hospital well and planned for re-challenge of TKI during follow-up.

## Discussion

Nilotinib, a second-generation TKI, has been shown in the ENESTnd study to induce more rapid and profound molecular responses than imatinib in patients with CML in the chronic phase (CML-CP).[2] The proxy measurements of molecular response, $MR^{1.0}$, $MR^{2.0}$, $MR^{3.0}$ and $MR^{4.5}$ are achieved better, and earlier on, during first-line treatment with nilotinib.[2] These measurements predict better overall survival in CML-CP,[2] yet no direct proven long-term overall survival benefit has been demonstrable for nilotinib vs imatinib.

Cardiovascular adverse events with nilotinib have raised concerns about long-term sequelae of drugs administered for decades with 5% to 13% of patients experiencing cardiovascular events with nilotinib.[3] In addition, metabolic effects such as hyperglycaemia, hyperlipidaemia, and increased body mass index have significant implications for cardiovascular outcome in patients treated with nilotinib.[2,4] Preliminary studies suggest nilotinib has detrimental effects on endothelial cell function in vitro and may accelerate atherosclerosis in addition to the metabolic effects.[5] Therefore, cardiovascular risk assessment needs to be integrated and regular monitoring is important especially in patients at high risk of cardiac disease. Our patient presented with acute coronary syndrome after 1 year of treatment with nilotinib. She was previously taking imatinib, but current evidence suggests a lower incidence of cardiovascular events in patients taking imatinib, even compared with those not taking TKIs (Table).[3] Early cardiac intervention and optimisation of risk factors may improve overall morbidity and mortality.

 

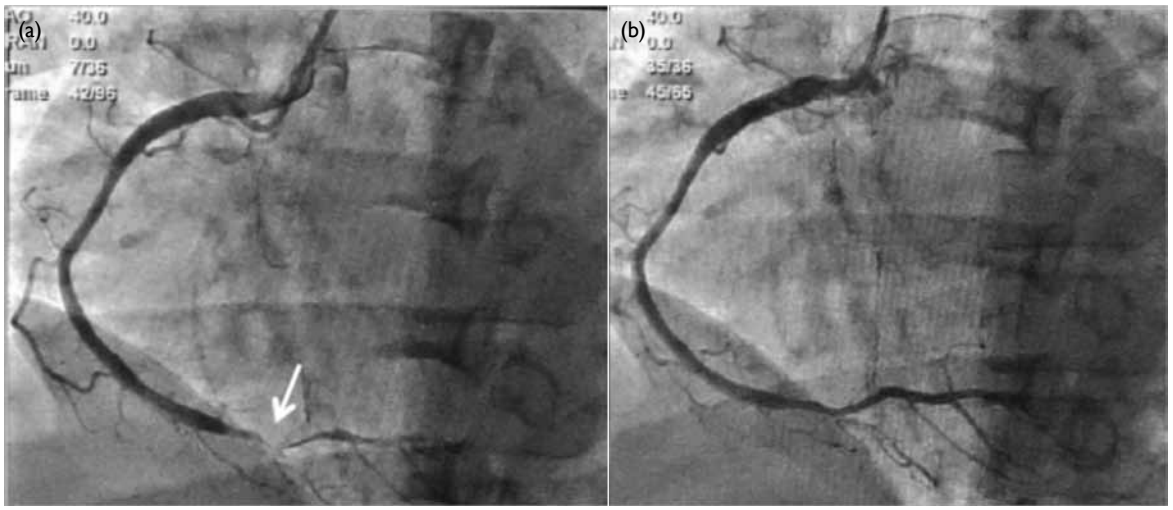


FIG. Angiograms showing (a) 95% distal right coronary artery stenosis (arrow) and (b) after successful angioplasty and stenting

In summary, cardiac events have been reported in CML patients treated with nilotinib. Therefore, it is important to recognise these possible complications. Early treatment can then be instituted to improve overall outcome.

TABLE. Potential cardiovascular events in association with different tyrosine kinase inhibitors[3]

| Tyrosine kinase inhibitor | Potential cardiovascular events |
|---|---|
| Imatinib | Congestive heart failure and left ventricular dysfunction |
| Nilotinib | QT prolongation and arrhythmia<br>Peripheral arterial occlusive disease<br>Ischaemic heart disease<br>Cerebrovascular disease |
| Dasatinib | Pulmonary arterial hypertension<br>Arterial ischaemic events |
| Ponatinib | Hypertension<br>Congestive heart failure<br>Peripheral arterial occlusive disease<br>Ischaemic heart disease<br>Cerebrovascular disease<br>Venous thromboembolism |

## Author contributions

All authors contributed to the concept, acquisition of data, analysis of data, drafting of the manuscript, and critical revision of important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

## Acknowledgements

The authors would like to thank the Director General of Health Malaysia for permission to publish this article.

## Conflicts of interest

All authors have disclosed no conflicts of interest.

## Funding/support

This paper received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Patient consent

The patient provided written consent for publication.

## References

1. Vardiman JW, Melo JV, Baccarani M, Thiele J. Chronic myelogenous leukaemia, BCR-ABL1 positive. In: Swerdlow SH, Campo E, Harris NL, et al, editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon: IARC; 2008: 32-7.
2. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010;362:2251-9.
3. Moslehi JJ, Deininger M. Tyrosine kinase inhibitor-associated cardiovascular toxicity in chronic myeloid leukemia. J Clin Oncol 2015;33:4210-8.
4. Rea D, Mirault T, Cluzeau T, et al. Early onset hypercholesterolemia induced by the 2nd-generation tyrosine kinase inhibitor nilotinib in patients with chronic phase-chronic myeloid leukemia. Haematologica 2014;99:1197-203.
5. Emir H, Albrecht-Schgoer K, Huber K, et al. Nilotinib exerts direct pro-atherogenic and anti-angiogenic effects on vascular endothelial cells: a potential explanation for drug-induced vasculopathy in CML. Blood 2013;122:257.