Original Study

Cardiovascular Events After Exposure to Nilotinib in Chronic Myeloid Leukemia: Long-term Follow-up

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Abstract

The present study evaluated the incidence of cardiovascular events (CVEs) in 63 chronic myeloid leukemia (CML) patients after long-term exposure to nilotinib. By considering the effect of cardiovascular risk factors and defining CVEs according to the current 2014 American College of Cardiology/American Heart Association recommendations, the present study attempted to overcome the previous limitations in reporting CVEs in CML patients.

Introduction: Nilotinib is a highly effective tyrosine kinase inhibitor in the treatment of chronic myeloid leukemia (CML). However, reports of cardiovascular toxicities caused by nilotinib have recently raised critical concerns. The aim of the present study was to evaluate the incidence of cardiovascular events (CVEs) and frequency of asymptomatic peripheral arterial disease (PAD) after long-term exposure to nilotinib. **Patients and Methods:** In the present retrospective cohort, we evaluated the incidence of CVEs in 63 CML patients treated with nilotinib. The results of Doppler ultrasound examination of the carotid and vertebral and lower extremity arteries with ankle-brachial index measurements were collected in asymptomatic patients. The clinical outcome was a composite endpoint of PAD, acute coronary events, stroke, heart failure, and cardiovascular death. **Results:** Sixty-three patients with a median age of 60 years were followed up for a median duration of 63 months. After a median nilotinib exposure of 49.30 months (range, 7.00-117.95 months), for a total exposure of 178.7 patient-years, 6 patients (9%) had experienced the clinical outcome. Four patients (8%) had abnormal arterial leg Doppler ultrasound findings. No significant lesions were reported in carotid/vertebral artery ultrasound examinations. Together, hypertension and low-density lipoprotein cholesterol $>$ 2 mmol/L significantly increased the risk of CVEs or abnormal ultrasound findings (odds ratio, 37.65; 95% confidence interval, 4.06-348.9). **Conclusion:** The incidence of CVEs and the frequency of asymptomatic PAD in this population was low, and CVEs were associated with cardiovascular risk factors. Aggressive risk factor modification and applying standard definitions for measuring cardiovascular outcomes might have contributed to the findings. Further prospective and adequately powered studies are needed to explore the effect of the cardiovascular risk profile on CVEs in CML patients taking nilotinib.

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Introduction

Blocking the BCR-ABL protein was the first successful use of tyrosine kinase inhibitors (TKIs) and has revolutionized the management of chronic myeloid leukemia (CML).[1] During the past decade, significant improvement has occurred in the survival rates of patients with CML, and the clinical picture of CML has changed from a fatal disease to a chronic condition, with life expectancies similar to those of the general population for patients responsive to treatment.[2,3]

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Despite the promising effect of imatinib in CML, nearly 20% of patients receiving imatinib do not achieve a complete cytogenetic response, and others can develop side effects or drug resistance over time.[4] Second-generation TKIs were first introduced to overcome the intolerance[5] or resistance to imatinib.[6] The second-generation TKI nilotinib as first-line treatment has resulted in faster and deeper response rates compared with therapy with imatinib.[7] Reports of peripheral arterial disease (PAD) and cardiovascular events (CVEs) in patients exposed to nilotinib, however, have raised concerns about the vascular toxicity of this drug.[8-10] The exact incidence and mechanism of CVEs in patients with CML receiving long-term TKI therapy remains unknown. The incidence of nilotinib-induced CVEs has been reported with a considerably wide range, 1.3% to 35%, depending on the outcomes measured in the studies.[11-13]

By describing the cardiovascular outcomes using the current 2014 American College of Cardiology/American Heart Association (ACC/AHA) recommendations for the definition of cardiovascular endpoints[14] and considering traditional patient cardiovascular risk factors, the present study aimed to overcome the current limitations in reporting CVEs in patients with CML and to evaluate the incidence of CVEs after long-term exposure to nilotinib.

Patients and Methods

We evaluated the incidence of CVEs in 63 CML patients treated at our institution with nilotinib. All patients exposed to nilotinib between February 2007 and December 2016 were included in the present study. These patients had received nilotinib at some point during CML treatment and were followed up at our institution every 3 to 6 months. Patients with previous exposure to ponatinib or exposure to ponatinib after nilotinib therapy were excluded. Asymptomatic patients with previous exposure to nilotinib routinely underwent screening with Doppler ultrasound examination of the carotid and vertebral arteries and lower extremity arteries with ankle-brachial index (ABI) measurements at our institution. The result of these tests were collected.

Information on cardiovascular risk factors was obtained during clinic visits or from a review of the patients' medical records. A history of excessive drinking was defined as drinking $>$ 10 drinks per week for women or $>$ 15 drinks per week for men. A sedentary lifestyle was defined as undertaking $<$30 min of physical activity and $<$ 3 times a week as physical activity $<$ 3 times per week for $\geq$ 30 minutes per session. Hypertension was defined as systolic blood pressure $\geq$ 140 mm Hg and/or diastolic blood pressure $\geq$ 90 mm Hg measured on 2 occasions or the use of antihypertensive medications. Diabetes mellitus was defined as fasting serum glucose $\geq$ 7 mmol/L or hemoglobin A1c of $\geq$ 6.5% on 2 occasions or the use of blood glucose-lowering medications. Dyslipidemia was defined as high low-density lipoprotein (LDL) cholesterol requiring treatment according to the Canadian Cardiovascular Society guidelines[15] or previous use of medication for dyslipidemia. A family history of premature cardiovascular disease (CVD) was defined as CVD in a male parent or sibling aged $<$ 55 years or a female parent or sibling aged $<$ 65 years. The patients' medical history was obtained by self-report during clinic visits and confirmed by medical record review.

All clinical outcomes were obtained by a review of the patients' medical records since the initiation of nilotinib until the last visit available in the electronic medical records (defined as the follow-up duration; Table 1). All clinical outcomes were defined using the 2014 ACC/AHA recommendations for defining cardiovascular endpoints in clinical trials.[14] The following clinical cardiovascular endpoints were measured and combined to create the composite endpoint for CVEs (clinical outcome): (1) acute coronary syndrome and hospitalization for unstable angina; (2) myocardial infarction; (3) chest pain and coronary artery disease (CAD) confirmed by angiography or the need for revascularization; (4) heart failure event; (5) symptomatic PAD managed medically or surgically and proved anatomically; and (6) cardiovascular death.

The Doppler ultrasound results for those patients who did not experience the clinical outcome were also collected (subclinical outcome). Abnormal Doppler ultrasound findings were defined as either an ABI $<$ 0.9 or severe lesions ($>$ 70%). When information was available, the Framingham CVD risk score (FRS)[16] was measured before the occurrence of CVEs or before the detection of abnormal ultrasound findings. The latest FRS was measured within 6 months of the study end date (June 2016 to December 2016) to define the current cardiovascular risk for the patients who had not experienced the clinical or subclinical outcome.

Statistical Analysis

Categorical variables were summarized as counts and percentages. Continuous variables were summarized as the mean $\pm$ standard deviation and/or median and range, as appropriate. The χ^2 association test was used to assess the effect of categorical clinical characteristics with the clinical outcome and/or ultrasound findings in the screened patients. Logistic regression analysis was also used to assessing the effect of the clinical and demographic variables of interest on the outcomes. The interval to the clinical outcome was calculated from the start date of nilotinib to the event date for CVEs and to the end of study period for those with no CVE. The Kaplan-Meier product limit method was used to estimate the 3- and 5-year event-free probability. $P < .05$ (2-sided) was considered statistically significant. All statistical analyses were undertaken using SAS, version 9.4, SAS System for Windows (SAS Institute, Inc, Cary, NC).

Results

Sixty-three patients (33 male and 30 female patients), with a median age of 60 years (range, 26-80 years), were studied and followed up for a median duration of 63 months (range, 8.54-117.95 months) from the first day of nilotinib treatment to the last visit available in the electronic medical records. The median duration of CML was 75.5 months (range, 14.49-347.47 months). The CML-associated baseline parameters, including previous TKI exposures, latest TKI, and median duration between nilotinib exposure and noninvasive vascular assessment using Doppler ultrasonography, are summarized in Table 1.

Of the 63 patients, 19 (30.16%) received only nilotinib during the study period. At the last visit 43 (68.25%) were taking nilotinib and 6 were off TKI. The cardiovascular risk factors, including age, gender, smoking, arterial hypertension, diabetes mellitus, body mass index, dyslipidemia, family history of premature CVD, excessive alcohol intake and sedentary lifestyle, are listed in Table 2.