Peripheral Artery Occlusive Disease Among Patients With Chronic Myeloid Leukemia Receiving Tyrosine Kinase Inhibitors: A Cross-Sectional Case-Control Study

Clinical Medicine Insights: Cardiology
Volume 11: 1–6
© The Author(s) 2017
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/1179546817747258

Thanawat Rattanathammethee[1], Adisak Tantiworawit[1], Ekarat Rattarittamrong[1], Chatree Chai-Adisaksopha[1], Sasinee Hantrakool[1], Arintaya Phrommintikul[2], Wanwarang Wongcharoen[2], Siriluck Gunaparn[2] and Lalita Norasetthada[1]

[1]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. [2]Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

ABSTRACT:

BACKGROUND: There were some reports of peripheral artery occlusive disease (PAOD) associated with nilotinib usage in chronic myeloid leukemia (CML). These complications in other tyrosine kinase inhibitors are revealed as unknown.

MATERIALS AND METHODS: We determined the prevalence of PAOD in patients with CML as compared with matched-control population by cross-sectional case-control study. Peripheral artery occlusive disease was screened by ankle-brachial index (ABI).

RESULTS: In total, 78 CML and 156 matched-control patients were included. The median age was 55 years. In all, 61 (78.2%) were on imatinib and 13 (16.7%) were on nilotinib, whereas 4 patients (5.2%) were on dasatinib. Prevalence of low ABI (<0.9) was 9.0%, and nilotinib users had the highest prevalence of low ABI of 30.7%. All cases with low ABI were not shown to be clinically overt of PAOD. There were well-balanced characteristics between cases of CML and matched control except in higher levels of hypercholesterolemia in the control. Interestingly, CML had more amounts of pathologic ABI than the control (odds ratio: 2.09, 95% confidence interval: 0.71-6.21), and diagnosis of diabetes found it to be independent of the risk of PAOD.

CONCLUSIONS: Peripheral artery occlusive disease was higher among patients with CML than the control, especially in patients who had diabetes.

KEYWORDS: Chronic myeloid leukemia, tyrosine kinase inhibitors, peripheral artery occlusive disease

RECEIVED: May 11, 2017. **ACCEPTED:** November 20, 2017.

TYPE: Original Research

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by the Thai Society of Hematology research grants.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Thanawat Rattanathammethee, Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. Email: thanawat_r@outlook.com

Introduction

Tyrosine kinase inhibitors (TKIs) are standard therapy in chronic myeloid leukemia (CML) individuals, especially for second-generation TKIs, and these inhibitors include nilotinib and dasatinib which pursue more cytogenetic and molecular response compared with imatinib.[1–5] Although the efficacy of newer TKIs has been proved, the association of TKIs with long-term complications has been of concern. There were a few studies among nilotinib-receiving patients who experienced peripheral artery occlusive disease (PAOD) and cardiovascular diseases.[6,7] Most of these were case reports and case series. Atherosclerotic risk modifications are essential for the prevention of these complications, and some of them require angioplasty. Nilotinib increases the risk of PAOD more than imatinib by 14.6 times, and a 10-year probability of being free from PAOD for imatinib and nilotinib was found to be 100% and 67%, respectively.[8] However, these studies had a small scale of population and lack of metabolic profiles and ankle-brachial index (ABI) for PAOD screening. Most of the previous studies on PAOD in CML individuals have revealed arterial occlusion to be clinically overt and recommended that the patients who had cardiovascular risk factors, for example, diabetes, hyperlipidemia, and hypertension, be screened for PAOD. This complication also brought about a decline in the quality of life and was related to many comorbidities.

In this study, we performed the cross-sectional case-control study to compare the prevalence of PAOD between patients with CML who were receiving TKIs and non-CML patients. All PAOD-related parameters were collected, and PAOD screening with ABI was performed.

Materials and Methods

This was a single-center, cross-sectional, case-control study of patients who were diagnosed with CML and were receiving

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

TKIs at Chiang Mai University Hospital between February 2014 and December 2014 in comparison with a control population in a 1:2 ratio with age, sex, and diabetes status matched. The study protocol was approved by the Institutional Review Board of Chiang Mai University and was conducted according to the Declaration of Helsinki. All patients provided written informed consent.

Patients and control population

All the study participants were adults (age >18 years) diagnosed with the chronic phase of CML and patients in Chiang Mai University Hospital. The clinical variables and the PAOD-related risk factors were recorded. Both the case and the control groups were screened to obtain ABI with the VaSera VS-1500N instrument (Fukuda Denshi Co Ltd, Tokyo, Japan). Ankle-brachial index values lower than 0.9 were classified into pathologic outcomes.[9] In cases of pathologic ABI, duplex ultrasound scan of lower legs or computed tomography angiogram was performed for confirming the diagnosis of PAOD.

Statistical analysis

According to previous reports on PAOD prevalence in patients with CML, the prevalence was found to be around 20%,[10,11] and for the general population, it reached 5%.[12] With the 2-sided significance level of .05 with at least 80% power, the planned sample size for the 1:2 ratio consisted of 76 patients and 152 patients for the case group and the control group, respectively. The subgroups were compared using χ^2 or Fisher exact test for categorical data and Mann-Whitney *U* test for quantitative data. Logistic regressions were applied to any significant values for multivariate analysis. A stratified Cox proportional hazards model was used to generate the odds ratio (OR) and 95% confidence interval (CI). The software used to obtain all the analytical values was SPSS for Mac version 20.

Results

Baseline characteristics

Between February 2014 and December 2014, the study enrolled 78 patients with CML with 156 control population as the planned 1:2 ratio. In our center, imatinib was first-line treatment of patients with CML. Nilotinib will be provided for imatinib failure or intolerance—so-called "second-line." Dasatinib switching is only for third-line treatment in previous failure or intolerance of nilotinib users. In all, 61 patients (78.2%) were on imatinib (all first line), 13 patients (16.7%) were on nilotinib (all second line), and 4 patients (5.1%) were on dasatinib (all third line). The median durations of the imatinib, nilotinib, and dasatinib treatments were 89.6, 46.7, and 22.1 months, respectively. Seventy-five patients (96.2%) were in the chronic phase of CML. Atherosclerotic risks included hypertension (20.5%), diabetes (12.8%), dyslipidemia (26.9%), metabolic syndrome (19.2%), and smoking (2.6%). The clinical variables and the PAOD-related risk factors are provided in Table 1. All the baseline characteristics were balanced between the TKI groups except that total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were prominent in the nilotinib and the dasatinib users compared with the imatinib users. For control population was matched with patients with CML by age, sex, and diabetes. This group had atherosclerotic risks including hypertension (21.8%), diabetes (12.8%), dyslipidemia (25.0%), and no smoking.

PAOD in patients with CML

There were 7 patients showing prevalence of 9.0% with pathologic ABI (Table 2, Figure 1). Patients receiving nilotinib had the highest prevalence of abnormal ABI of 30.8%, whereas patients receiving imatinib and dasatinib had prevalence of 4.9% and 0%, respectively. Nilotinib-using patients had augmented risk of PAOD, according to the ABI screening, compared with imatinib (OR: 8.59; 95% CI: 1.64-44.89; $P = .004$). For the multivariate analysis, there was only the independent factor of hemoglobin A_{1C} (HbA_{1C}) over 7 g/dL (OR: 2.41; 95% CI: 1.11-5.25; $P = .026$) which was positively associated with low ABI. All the 7 patients were asymptomatic and also achieved major molecular response ($MR^{3.0}$) by real-time quantitative polymerase chain reaction. The median age was 70 (50-86) years. Four were used to nilotinib usage with a median duration of 62 (55-67) months. Vascular imaging was performed, but only 2 patients who received nilotinib had significant stenosis of lower limb arteries (Table 1S). Because all of the patients did not have limb ischemia clinically, the vascular surgeons settled on conservative methods with atherosclerosis risk factor modification and closed monitoring.

PAOD prevalence compared with control population

Age, sex, and diabetes status of the control population were well matched with the patients with CML, but the control group had higher LDL-C and lower HDL-C levels (Table 3, Figure 2). However, the patients with CML, eventually, were found to have more prevalence of PAOD with OR of 2.09 (95% CI: 0.71-6.21; $P = .181$) by ABI.

Discussion

This study was the first to report prevalence of PAOD in patients with CML in Thailand, which was 9% by ABI. The gold standard of PAOD detection is the use of angiogram; however, that method is invasive, carries the risk of contrast-induced nephropathy, and might be exposed to anaphylactoid

Table 1. Clinical variables and PAOD-related risk factors in patients with CML.

VARIABLES	CASE, TOTAL N=78 (%)	IM N=61 (%)	NIL N=13 (%)	DAS N=4 (%)	*P* VALUE
Age, y, median (range)	55 (21-86)	54 (21-83)	68 (25-86)	60 (52-81)	.053
Male gender	41 (52.6)	33 (54.1)	6 (46.2)	2 (50)	.868
BMI, kg/m^2, median (range)	22.8 (14.4-31.3)	23.4 (17.3-31.3)	22.2 (14.4-28.8)	21.0 (19.5-25.5)	.218
Previous medical illness					
Hypertension	16 (20.5)	13 (21.3)	3 (23.1)	—	.888[a]
Diabetes mellitus	10 (12.8)	7 (11.5)	3 (23.1)	—	.267[a]
Dyslipidemia	21 (26.9)	13 (21.3)	6 (46.2)	2 (50)	.108
Concurrent medications					
Antihypertensive	9 (11.5)	8 (13.1)	1 (7.7)	—	.587[a]
Antiplatelet	2 (2.6)	2 (3.3)	—	—	—
Lipid-lowering agents	4 (5.1)	3 (4.9)	1 (7.7)	—	.688[a]
Blood chemistry, median					
FPG, mg/dL	96 (77-222)	95 (80-165)	90 (77-222)	100 (98-111)	.475
HbA_{1C}, g/dL	5.5 (4.2-10.5)	5.4 (4.2-9.4)	5.7 (4.6-10.5)	5.4 (4.7-5.8)	.133
Triglycerides, mg/dL	107 (39-2371)	105 (39-2371)	124 (56-228)	130.5 (79-273)	.752
Total cholesterol, mg/dL	166 (81-318)	154 (81-297)	206 (137-318)	223 (217-230)	<.001
LDL-C, mg/dL	99.5 (25-233)	92 (25-185)	135 (80-233)	157.5 (152-168)	<.001
HDL-C, mg/dL	51 (23-92)	51 (23-92)	58 (47-91)	48 (31-56)	.037
Metabolic syndrome	15 (19.2)	12 (19.7)	2 (15.4)	1 (25)	.897
Duration of TKI, mo, median (range)	80 (3-233)	89.6 (1.9-194)	46.7 (2.9-67)	22.1 (4.7-45.3)	<.001
Line of treatment					<.001
First line	61 (78.2)	61 (100)	—	—	
Second line	13 (16.7)	—	13 (100)	—	
Third line	4 (5.1)	—	—	4 (100)	

Abbreviations: BMI, body mass index; CML, chronic myeloid leukemia; DAS, dasatinib; FPG, fasting plasma glucose; HbA_{1C}, hemoglobin A_{1C}; HDL-C, high-density lipoprotein cholesterol; IM, imatinib; LDL-C, low-density lipoprotein cholesterol; NIL, nilotinib; PAOD, peripheral artery occlusive disease; TKI, tyrosine kinase inhibitor.
[a]When comparing only the IM group with the NIL group.

Table 2. Seven cases of CML with pathologic ABI (<0.9).

SUBJECT[a]	VASCULAR IMAGING	GENDER/AGE	DM/HT/DLP	TKIS, MG/D, DURATION
006	CTA: normal	F/50	–/–/–	IM-400, 116 mo
035	Ultrasound Doppler: normal	M/59	+/+/–	IM-400, 119 mo
072	Ultrasound Doppler: normal	M/58	–/+/+	IM-400, 42 mo
012	Ultrasound Doppler: positive[b]	F/73	–/+/+	NIL-800, 62 mo
043	CTA: positive[b]	M/86	–/–/–	NIL-800, 67 mo
010	Ultrasound Doppler: normal	F/55	–/–/+	NIL-800, 55 mo
091	Ultrasound Doppler: normal	M/70	+/–/–	NIL-800, 62 mo

Abbreviations: CML, chronic myeloid leukemia; CTA, computed tomography angiography; DLP, dyslipidemia; DM, diabetes mellitus; F, female; HT, hypertension; IM, imatinib; M, male; NIL, nilotinib; TKIs, tyrosine kinase inhibitors.
– indicates nondiagnosed; + indicates diagnosed.
[a]All subjects were asymptomatic and MMR (major molecular response, $MR^{3.0}$ by real-time quantitative polymerase chain reaction method).
[b]Occlusion or significant stenosis of lower leg arteries.

reaction with infusional contrast media. Less invasive procedures have been invented in various methods, with one of the most generally used being ABI. Peripheral artery occlusive disease screening by ABI has given values lower than 0.9, with sensitivity in the range of 15% to 79%, specificity in the range of 83.3% to 99%, and accuracy in the range of 72.1% to 89.2%.[9] The prevalence of PAOD in this study was less than that reported by previous reports which predominantly measured the same by ABI, and the average was 20%. This might be explained by the difference in ethnicities, body mass indexes, cardiovascular risk factors, and numbers of populations in the various studies. For the risk of PAOD among 3 kinds of TKIs, nilotinib uncovered an OR of 8.59 (95% CI: 1.64-44.89; $P = .004$) which harmoniously correlates to the findings of previous studies which reported about 10.3-fold to 14.6-fold higher risk of PAOD in the case of nilotinib compared with imatinib.[13] Recently, a review of PAOD screening in patients using only nilotinib showed abnormal ABI or pulse wave velocity in 19.3%,[14] which strongly implicates nilotinib therapy as being proatherogenic. Moreover, results of pathologic ABI have reported up to 3.2-fold increase in cardiovascular morbidities in type 2 diabetes,[15] and we also found that the only independent risk for PAOD was HbA_{1C} being more than 7 g/dL (OR: 2.41; 95% CI: 1.11-5.25; $P = .026$). This finding reveals the close relationship between PAOD and diabetes mellitus, too. Some of the previous reports of PAOD in CML in comparison with this study are presented in Table 4.

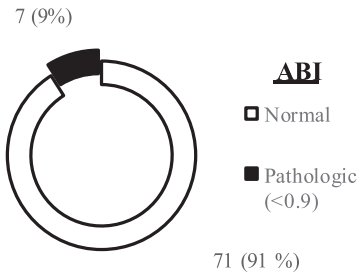

Figure 1. Peripheral artery occlusive disease prevalence in patients with chronic myeloid leukemia, n = 78. ABI indicates ankle-brachial index.

With reference to earlier PAOD screening development, stiffness of vasculature was the one of the interests. The arterial stiffness usually appears before vascular obstruction. This is because the inflammatory process causes intima media degradation, increase in collagen, calcification, and proteolytic enzymes, resulting in elastin damage and arterial occlusion.[16] However, the method of measuring arterial stiffness is not widely used because of inconclusive data for cutoff level and the procedure not being available in most of the centers in our country.

The effect of protein kinase inhibition on endothelium and myocardium has been studied in patients with metastatic renal cell carcinoma who used sunitinib and sorafenib as TKIs for the therapeutic scheme. These studies showed evidence of vasculopathies with circulatory disturbance.[17–19] As far as nilotinib is concerned, it not only inhibited KIT kinase and PDGFR kinase, which are actions similar to imatinib, but also inhibited the discoidin domain receptor 1 (DDR1) which resulted in plaque formation and atherosclerosis in mouse models.[20] The cellular mechanism of DDR1 inhibition also enhanced the

Table 3. Peripheral artery occlusive disease prevalence compared with control population[a].

DATA	CASE (N = 78)	CONTROL (N = 156)	*P* VALUE
Age, y	55 (21-86)	54 (21-83)	.342
Male gender	52.6	52.6	1.000
BMI, kg/m^2	22.8 (14.4-31.3)	23.7 (15.4-40.4)	.085
Previous illness			
Hypertension	20.5	21.8	.822
Diabetes mellitus	12.8	12.8	1.000
Dyslipidemia	26.9	25.0	.751
Blood chemistry, mg/dL			
FPG	96 (76-222)	99 (79-231)	.249
Triglycerides	107 (39-2371)	108 (37-603)	.835
Total cholesterol	166 (81-318)	204 (51-363)	.178
LDL-C	99.5 (25-233)	138 (56-289)	.018
HDL-C	51 (23-92)	48 (17-92)	.014

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a]Values are expressed as median (range) or percentages.

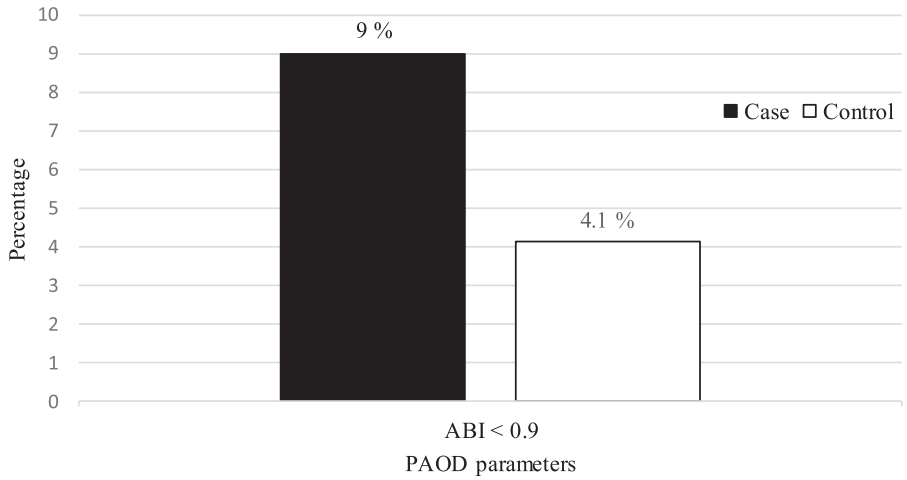

Figure 2. Comparison of PAOD prevalence between cases of chronic myeloid leukemia and the control group. ABI indicates ankle-brachial index; PAOD, peripheral artery occlusive disease.

Table 4. Previous reports on PAOD in CML.

TRIALS	STUDY DESIGN	RESULTS
Giles et al[10]	Retrospective IM = 1301, NIL = 556, no TKIs = 533 Clinically overt PAOD, n = 12 (IM = 2, NIL = 7, no TKIs = 3)	NIL vs IM (OR: 14.5, 95% CI: 2.7-145.6) NIL vs no TKIs (OR: 0.9, 95% CI: 0.2-5.4) IM vs no TKIs (OR: 0.06, 95% CI: 0.005-0.5) Conclusion: NIL increased PAOD risk, and IM might be a protective factor
Kim et al[11]	Prospective cohort IM = 54, NIL = 66 Clinically overt PAOD, n = 24 (IM = 3, NIL = 17)	NIL vs IM (OR: 10.3, 95% CI: 2.3-61.5) NIL arm had older-age patients, more dyslipidemia Conclusion: NIL increased PAOD risk
Lee et al[14]	Retrospective NIL = 88 Abnormal ABI or PWV, n = 17 (Cutoff level of ABI <1.0)	Pathologic ABI (<0.9) = 1/17 (6%) Pathologic arterial stiffness by PWV (1200-2000 cm/s adjusted by age) = 8/17 (47%)
This study	Cross-sectional case-control PAOD screening by ABI n = 78 (case), n = 156 (control) IM = 61, NIL = 13, DAS = 4 All were asymptomatic PAOD, n = 7 (IM = 3, NIL = 4)	NIL vs IM (OR: 8.59; 95% CI: 1.6-44.9) Diabetes mellitus increased risk of PAOD Trend of more PAOD prevalence in CML cases

Abbreviations: CI, confidence interval; CML, chronic myeloid leukemia; DAS, dasatinib; IM, imatinib; NIL, nilotinib; OR, odds ratio; PAOD, peripheral artery occlusive disease; PWV, pulse wave velocity; TKIs, tyrosine kinase inhibitors.

possibility of diabetes mellitus with evidence of elevated serum amylase and beta cells indicative of dysfunction of the pancreas.[21] Nilotinib may exert proatherogenic and antiangiogenic effects on endothelial cells. Arterial stenosis resulting from the proatherogenesis and the antiangiogenesis of the drug may inhibit the repair mechanism of recanalization and reperfusion.[22] Recently, a review on vascular adverse events (VAEs) in TKI-treated patients with CML also reported the frequency of VAEs in nilotinib users as being in the range of 1% to 29%, including PAOD in 1% to 20%, and it also found the number of patients developing VAEs increasing over time.[23]

To the best of our knowledge, this study was the first case-matched control design study on PAOD risk factor assessment in CML. Interestingly, matched control of age and diabetes had greater LDL-C and lower HDL-C levels, and the PAOD prevalence in CML individuals appeared to be higher for ABI among various kinds of TKIs patients with in CML. Hypercholesterolemia might not be a PAOD predictive risk, or TKIs may play a greater role in vascular inflammation than higher levels of cholesterol in circulation. However, the type of TKI was not found to have an influence on PAOD risk when analyzed using multivariate analysis.

Limitations

This was a cross-sectional case-control, single-institution study that had a small sample size. Because of the limited resources and reimbursement issues in our center, imatinib was the only first choice for therapy in patients with chronic phase CML, with the second line of treatment and the third line of treatment being scheduled on nilotinib and dasatinib, respectively. There was inequality in the number of patients between the 3

kinds of TKIs, which might have caused misleading in the interpretation of results. This trial was not analysed on sex and aged effects causing PAOD, menopause or andropause might be related factors, number of subjects was inadequate power. Larger number of subjects should be provided to address these outcomes.

Conclusions

The investigation regarding prevalence of PAOD using ABI found that it was higher among patients with CML than in the control population. Patients with CML receiving TKIs and who had diabetes have a higher chance of developing PAOD and should be carefully monitored for this complication. Peripheral artery occlusive disease screening might be made pretreatment schema for patients with CML who have levels of HbA_{1C} higher than 7 g/dL, especially in cases where nilotinib is planned to be included in the long-term treatment.

Acknowledgements

The authors thank all of the patients who participated in this study and collaborators from the Division of Cardiology, Department of Internal Medicine, Chiang Mai University, Thailand, who provided the facilities.

Author Contributions

TR, AT, ER, CC-A, SH, AP, WW, SG, and LN conceived and designed the experiments; agree with manuscript results and conclusions; jointly developed the structure and arguments for the paper; made critical revisions and approved final version; and reviewed and approved the final manuscript. TR, AP, WW, and LN analyzed the data. TR, AT, ER, and LN wrote the first draft of the manuscript. TR, AT, ER, AP, and LN contributed to the writing of the manuscript.

REFERENCES

1. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362:2251–2259.
2. Larson RA, Hochhaus A, Hughes TP, et al. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. *Leukemia*. 2012;26:2197–2203.
3. Branford S, Kim DW, Soverini S, et al. Initial molecular response at 3 months may predict both response and event-free survival at 24 months in imatinib-resistant or -intolerant patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase treated with nilotinib. *J Clin Oncol*. 2012;30:4323–4329.
4. Larson RA, Hochhaus A, Saglio G, et al. Nilotinib versus imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): ENESTnd 4-year update. *J Clin Oncol*. 2013;31: Abstract 7052.
5. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010;362:2260–2270.
6. Aichberger KJ, Herndlhofer S, Schernthaner GH, et al. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. *Am J Hematol*. 2011;86:533–539.
7. Tefferi A, Letendre L. Nilotinib treatment-associated peripheral artery disease and sudden death: yet another reason to stick to imatinib as front-line therapy for chronic myelogenous leukemia. *Am J Hematol*. 2011;86:610–611.
8. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA guidelines for the management of patients with peripheral arterial diseases. *Circulation*. 2006; 113:e463–e654.
9. Xu D, Li J, Zou L, et al. Sensitivity and specificity of the ankle-brachial index to diagnose peripheral artery disease: a structured review. *Vasc Med*. 2010;15: 361–369.
10. Giles FJ, Mauro MJ, Hong F, et al. Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: a retrospective cohort analysis. *Leukemia*. 2013;27:1310–1315.
11. Kim TD, Rea D, Schwarz M, et al. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. *Leukemia*. 2013;27:1316–1321.
12. Sritara P, Sritara C, Woodward M, et al. Prevalence and risk factors of peripheral arterial disease in a selected Thai population. *Angiology*. 2007;58:572–578.
13. Levato L, Cantaffa R, Kropp MG, Magro D, Piro E, Molica S. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in chronic myeloid leukemia: a single institution study. *Eur J Hematol*. 2013;90:531–532.
14. Lee SE, Choi SY, Kim SH, et al. Peripheral arterial occlusive disease (PAOD) in chronic phase chronic myeloid leukemia patients treated with nilotinib. *Blood*. 2013;122:4018.
15. Bundo M, Munoz L, Perez C, et al. Asymptomatic peripheral arterial disease in type 2 diabetes patients: a 10-year follow-up study of the utility of the ankle brachial index as a prognostic marker of cardiovascular disease. *Ann Vasc Surg*. 2010;24:985–993.
16. Yasmin M, McEniery CM, O'Shaughnessy KM, et al. Variation in the human matrixmetalloproteinase-9 gene is associated with arterial stiffness in healthy individuals. *Arterioscler Thromb Vasc Biol*. 2006;26:1799–1805.
17. Kappers MH, de Beer VJ, Zhou Z, et al. Sunitinib-induced systemic vasoconstriction in swine is endothelin mediated and does not involve nitric oxide or oxidative stress. *Hypertension*. 2012;59:151–157.
18. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet*. 2007;370:2011–2019.
19. Schmidinger M, Zielinski CC, Vogl UM, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2008;26:5204–5212.
20. Ferri N, Carragher NO, Raines EW. Role of discoidin domain receptors 1 and 2 in human smooth muscle cell-mediated collagen remodeling: potential implications in atherosclerosis and lymphangioleiomyomatosis. *Am J Pathol*. 2004;164:1575–1585.
21. Franco C, Ahmad PJ, Hou G, Wong E, Bendeck MP. Increased cell and matrix accumulation during atherogenesis in mice with vessel wall-specific deletion of discoidin domain receptor 1. *Circ Res*. 2010;106:1775–1783.
22. Hadzijusufovic E, 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:Abstract 257.
23. Valent P, Hadzijusufovic E, Schernthaner GH, Wolf D, Rea D, Coutre P. Vascular safety issues in CML patients treated with BCR/ABL1 kinase inhibitors. *Blood*. 2015;125:901–906.