VOLUME 33 · NUMBER 35 · DECEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Tyrosine Kinase Inhibitor–Associated Cardiovascular Toxicity in Chronic Myeloid Leukemia

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Published online ahead of print at www.jco.org on September 14, 2015.

Supported by grants from the Leukemia and Lymphoma Society (M.D.), the National Institutes of Health (Grants No. R01CA178397-01A1, P01CA049639, and P30CA042014; M.D.), the V Foundation (M.D.), and the National Heart, Lung and Blood Institute (Grant No. K08HL09703; J.J.M.).

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Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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0732-183X/15/3335w-4210w/$20.00

DOI: 10.1200/JCO.2015.62.4718

ABSTRACT

For most patients with chronic myeloid leukemia, tyrosine kinase inhibitors (TKIs) have turned a fatal disease into a manageable chronic condition. Imatinib, the first BCR-ABL1 TKI granted regulatory approval, has been surpassed in terms of molecular responses by the second-generation TKIs nilotinib, dasatinib, and bosutinib. Recently, ponatinib was approved as the only TKI with activity against the T315I mutation. Although all TKIs are associated with nonhematologic adverse events (AEs), experience with imatinib suggested that toxicities are typically manageable and apparent early during drug development. Recent reports of cardiovascular AEs with nilotinib and particularly ponatinib and of pulmonary arterial hypertension with dasatinib have raised concerns about long-term sequelae of drugs that may be administered for decades. Here, we review what is currently known about the cardiovascular toxicities of BCR-ABL1 TKIs, discuss potential mechanisms underlying cardiovascular AEs, and elucidate discrepancies between the reporting of such AEs between oncology and cardiovascular trials. Whenever possible, we provide practical recommendations, but we concede that cause-directed interventions will require better mechanistic understanding. We suggest that chronic myeloid leukemia heralds a fundamental shift in oncology toward effective but mostly noncurative long-term therapies. Realizing the full potential of these treatments will require a proactive rational approach to minimize long-term cardiovascular and cardiometabolic toxicities.

J Clin Oncol 33:4210-4218. © 2015 by American Society of Clinical Oncology

TARGETING BCR-ABL1 IN CHRONIC MYELOID LEUKEMIA

Aberrant activation of tyrosine kinases is implicated in multiple cancers and has stimulated intense efforts to develop tyrosine kinase inhibitors (TKIs) for therapy.[1] Chronic myeloid leukemia (CML), a myeloproliferative neoplasm caused by BCR-ABL1, was the first malignancy successfully treated with a TKI, imatinib.[2] With imatinib, 5-year survival rates of patients with newly diagnosed CML increased from 40% to 50% to 90%[3]; survival of patients with a complete cytogenetic response is comparable to that of age-matched controls.[4] Second-generation (2G) TKIs, initially developed to overcome imatinib resistance, were subsequently shown to induce more rapid and profound molecular responses; nilotinib and dasatinib were approved for front-line therapy, whereas bosutinib failed in the primary end point of a front-line study and is currently a second-line agent.[5-7] Ponatinib, a third-generation (3G) TKI, is the only clinical TKI active against the BCR-ABL1^{T315I} mutation.[8,9] Ponatinib was initially approved in the United States with a fairly broad label, but after reports of cardiovascular toxicity, its indication was restricted to patients with the BCR-ABL1^{T315I} mutation or in whom other TKIs are not indicated.[10]

Despite improved response kinetics and reduced progression rates in patients started on 2G TKIs, overall survival is so far comparable to patients started on imatinib.[5,6] This may reflect effective salvage for imatinib treatment failure or indicate that observing a significant difference will require longer follow-up. Alternatively, mortality from non-CML causes could offset survival gains afforded by the increased efficacy of 2G TKIs. Some patients on imatinib achieve sustained deep molecular responses. Discontinuation trials have shown that 40% to 50% of these patients maintain responses without continued therapy, suggesting that a fraction of patients may be cured with TKIs.[11-13] There is hope that the higher deep molecular response rates with 2G TKIs will translate into a higher percentage of successful treatment-free remissions. However, the reality in 2015 is that most patients with CML will require long-term TKI therapy. Because the median age at CML diagnosis in the Western world is greater than 60 years, when cardiovascular disease is common, the cardiovascular effects of BCR-ABL1 TKIs are critical factors in therapy decisions.

Kinase/TKI	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib	Sorafenib	Sunitinib
ABL1	100	105	83	98	101	46	92
ABL1(T315I)	93	68	9	15	100	53	97
FGFR1	79	47	0	0	101	78	93
FGFR2	95	73	3	0	100	91	97
FGFR3	83	34	1	0	101	76	97
FGFR4	3	9	8	0	98	19	55
FLT1 (VEGFR1)	97	39	5	0	101	99	98
FLT3	77	17	68	60	99	100	100
FLT4 (VEGFR3)	92	31	3	17	101	97	99
KDR (VEGFR2)	101	22	7	22	94	99	98
KIT	23	100	97	96	101	98	98
PDGFRα	77	100	98	103	103	100	98
PDGFRβ	95	99	91	93	102	98	99
SRC	96	101	5	23	102	12	84
TIE2	22	16	0	41	101	29	21

Fig 1. Activity of approved ABL1 tyrosine kinase inhibitors (TKIs; bosutinib, dasatinib, imatinib, nilotinib, ponatinib), sorafenib, and sunitinib against tyrosine kinases with a known function in vascular biology, ABL1 and ABL1^{T315I}. The numbers represent percent inhibition of kinase activity at 1 μmol/L of inhibitor. Reported values less than 0 were set to 0. Red indicates 96% to 100% inhibition; gold indicates 51% to 95% inhibition; and blue indicates 0% to 50% inhibition. Data adapted.[14]

BCR-ABL1 TKI EFFECTS ON VASCULAR SYSTEM KINASES

Although all TKIs approved for CML therapy share activity against BCR-ABL1, they are distinct in their potency and activity against other kinases, including those involved in vascular biology such as vascular endothelial growth factor receptors (VEGFR) 1 to 3, TIE-2, platelet-derived growth factor receptors A and B (PDGFRA/B), and fibroblast growth factor receptors (FGFR) 1 to 4 (Fig 1).[14] Pull-down experiments on whole-cell lysates have also identified nonkinase targets (eg, oxidoreductase NQO2 for nilotinib and imatinib), further complicating the molecular causality assessment of adverse events (AEs).[15,16] Additional critical determinants of TKI activity against both the intended target and undesired targets are plasma half-life, peak and trough concentrations, and protein binding (Appendix Table A1, online only). Clinically, TKIs are selected based on disease characteristics, expected AEs, comorbidities, and patient preference.[17] Despite speculation about correlations between certain off-target activities and AEs, AE management remains empirical.[18] This seemed acceptable, as long as severe nonhematologic toxicities were reversible and occurred early, while patients were still under close surveillance. Reports of cardiovascular AEs with nilotinib,[19,20] pulmonary arterial hypertension (PAH) on dasatinib,[21] and frequent cardiovascular AEs with ponatinib have caused a reassessment of the situation.[10,22]

IMATINIB: BENCHMARKING TKI EFFICACY AND LONG-TERM TOXICITY

Imatinib was first developed as an inhibitor of PDGFR but was subsequently shown to inhibit ABL1 and KIT.[23,24] No maximum-tolerated dose was determined in CML, whereas GI AEs established 800 mg per day as the maximum-tolerated dose in GI stromal tumors.[2,25] The International Randomized Interferon Versus STI571 (IRIS) study (Appendix Table A2, online only) of patients with newly diagnosed CML confirmed imatinib's favorable safety profile.[3,26] Despite many nonhematologic AEs, at 5 years of follow-up, only 4% of patients had discontinued imatinib as a result of AEs, whereas the projected overall survival was at an unprecedented 89%, establishing imatinib as an efficacy and safety benchmark.[3]

In 2006, Kerkela et al[27] reported in vitro and murine studies suggesting imatinib caused toxic cardiomyopathy. Ectopic expression of ABL1^{T315I} rescued cardiomyocytes from imatinib-induced death, implicating c-Abl inhibition in cardiotoxicity.[27] The motivation for this study was a single-institution series of 10 patients who developed left ventricular dysfunction on imatinib. However, the population incidence of imatinib-associated cardiomyopathy was not reported, and the causal relationship to imatinib remained unclear.[28-31] Subsequent long-term observations in patients on imatinib showed a low incidence of cardiomyopathy. In the IRIS trial, for example, only one patient (< 1%) had developed congestive heart failure at 5 years.[3] Prospective and sequential cardiac imaging in patients on imatinib showed a low incidence of asymptomatic cardiac dysfunction, comparable to the expected population incidence.[32-35] The discordance between mice and men may be explained by different cardiovascular physiologies or by the high doses of imatinib used by Kerkela et al[27] (50 to 200 mg/kg per day, equivalent to 3.5 to 14 g per day in humans).[27,36,37]

Imatinib may have favorable metabolic and vascular effects. In prediabetic and new-onset diabetic mice, imatinib prevented and reversed type 1 diabetes and attenuated diabetes-induced atherosclerosis, possibly as a result of PDGFR inhibition.[38,39] In humans, this beneficial metabolic effect has only been seen in isolated cases.[40-42] Retrospective analysis of phase III studies has revealed a lower incidence of cardiovascular events in patients treated with imatinib versus nilotinib and compared with patients treated without TKIs, raising the possibility that imatinib is protective, but prospective controlled comparisons versus age-matched controls are lacking.[20] In animal models, imatinib reversed experimentally induced PAH.[43] In one trial, adding imatinib to conventional PAH therapy improved exercise capacity and hemodynamics[44,45]; however, tolerance was poor as a result of previously reported AEs, and there was an unusually high rate of subdural hematomas.[44]

The cardiovascular experience with imatinib introduces several important concepts that are particularly relevant to the newer TKIs. First, given the excellent prognosis of CML and the high incidence of cardiovascular disease in the general population, it is important to dissect drug-dependent from drug-independent cardiovascular events. Because retrospective studies are prone to reporting bias, future clinical trials should prospectively incorporate cardiovascular and cardiometabolic end points. Second, defining the cardiovascular baseline risk of the specific CML population under study is crucial. Third, because cardiovascular disease develops as a result of risk factors

accumulated over years, short-term assessments of established risk factors and long-term follow-up for specific cardiovascular end points are necessary to understand the cardiovascular sequelae of each TKI. Fourth, systematic prospective assessment of cardiovascular risk factors is needed as newer TKIs are compared with imatinib as the benchmark for efficacy and cardiovascular risk. Fifth, oncology trials may offer a platform to investigate potential beneficial cardiovascular and cardiometabolic TKI effects. Using this platform will require close collaborations between cardiologists and oncologists, both in clinical trial design and in adjudicating cardiovascular end points. Finally, preclinical studies must be complemented with stringent studies in humans. The fact that many of these issues were insufficiently considered when 2G and 3G TKIs were developed has hampered the development of rational strategies to prevent and treat cardiovascular AEs.

CARDIOVASCULAR SAFETY OF 2G AND 3G TKIs

Dasatinib

Dasatinib was initially approved for salvage treatment and subsequently for front-line CML therapy, based on superior 12-month complete cytogenetic response rates compared with imatinib (Dasatinib Versus Imatinib Study in Treatment-Naïve CML Patients [DASISION] study).[46,47] The nonhematologic safety profile was similar to imatinib with the exception of frequent pleural effusions.[47] A first case of dasatinib-associated PAH was reported in 2009.[48] In 2012, the French Pulmonary Hypertension Registry reported nine patients with dasatinib-associated PAH.[21] At PAH diagnosis, patients had moderate to severe precapillary pulmonary hypertension, with severe symptoms and hemodynamic compromise. In keeping with dasatinib being the cause, improvements were observed after TKI withdrawal, but two patients died in follow-up as a result of sudden death or cardiac failure. No patients on other TKIs were noted in the registry, and the frequency of dasatinib-associated PAH was estimated to be at least 0.45%. At 36 months of follow-up of the DASISION study, PAH was reported in 3% of patients on dasatinib and 0% on imatinib. PAH was confirmed with echocardiography, although only one patient (of eight patients) underwent definitive work-up with right heart catheterization.[6]

In October 2011, the US Food and Drug Administration (FDA) issued a warning regarding cardiopulmonary risks of dasatinib and recommended that patients be evaluated for signs and symptoms of cardiopulmonary disease before and during dasatinib treatment.[49] Because dyspnea is nonspecific, more common causes of dasatinib-associated dyspnea (eg, pleural effusion, anemia) should be ruled out before an invasive PAH work-up. Although the FDA did not specify modes of screening, we believe that an echocardiogram with Doppler flow studies would provide adequate noninvasive assessment for high-risk patients before starting dasatinib and for patients with cardiopulmonary symptoms on treatment. Patients suspected of having PAH should be referred to a cardiologist.

Whether dasatinib increases the risk for cardiovascular events is not entirely clear. In early clinical trials involving dasatinib, there was no concerning signal of peripheral vascular events.[50] However, the final analysis of the DASISION trial with 5-year follow-up found a slightly higher risk of arterial ischemic events in patients on dasatinib (5%) compared with imatinib (2%). In contrast, a retrospective analysis of patients treated with dasatinib for CML or prostate cancer found that cardiovascular ischemic events were not higher than standardized incidence rates,[51] which may point to a protective effect of imatinib in the DASISION study. Only prospective studies will be able to definitively clarify the question.

Nilotinib

Initially a second-line agent, nilotinib was approved for patients with newly diagnosed CML based on higher 12-month major molecular response rates and reduced progression compared with imatinib (Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients [ENESTnd] study).[32,52] Detailed electrocardiograms performed during the phase I clinical trial revealed a 5- to 15-millisecond prolongation in the corrected QT interval in a subset of patients.[52] As a result, careful monitoring for arrhythmias and strict avoidance of QT interval–prolonging medications were recommended.[52] Since FDA approval, there has been no additional signal suggesting ventricular arrhythmias as a result of QT prolongation.[5,53] Serial echocardiograms during ENESTnd revealed no evidence for cardiomyopathy.[32] However, 36% of patients on nilotinib 300 mg twice per day experienced hyperglycemia compared with 20% on imatinib; rates of grade 3 or 4 hyperglycemia (blood glucose $>$ 250 mg/dL) were 6% versus 0%. Subsequent studies revealed an association with increased body mass index.[54] Nilotinib was also associated with hyperlipidemia in the ENESTnd study, and a recent prospective study of 27 patients showed a significant increase of total, low-density lipoprotein, and high-density lipoprotein cholesterol within 3 months of treatment.[55]

Several recent studies have reported vascular toxicity with nilotinib (Table 1). In a retrospective multicenter analysis of 179 patients, 11 patients (6.2%) developed peripheral arterial disease (PAD) involving lower limbs. Most striking was the severity of PAD; eight patients required invasive therapy (angioplasty and stent placement), and four patients required amputation.[56] A single-center study of 24 patients reported PAD in three patients, all requiring angioplasty or surgery.[19] A number of other retrospective studies from single institutions have confirmed a higher than expected incidence of peripheral or cardiac ischemic events in patients treated with nilotinib (Table 1). The finding that cardiovascular risk factors were common in patients with vascular AEs, combined with the elevations in glucose and cholesterol, suggested that nilotinib may aggravate a pre-existing arteriosclerotic condition. In a meta-analysis of the IRIS, Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS), and ENESTnd studies, peripheral arterial occlusive disease (PAOD) was reported in seven (1.3%) of 556 patients treated with nilotinib, three (0.6%) of 533 patients treated with no TKI, and two (0.2%) of 1,301 patients treated with imatinib.[20] A 3-year follow-up of the ENESTnd trial suggests a higher incidence of vascular events in patients treated with nilotinib compared with imatinib; eight (1.4%) of 556 and 11 (2.0%) of 556 nilotinib-treated patients had PAOD and ischemic heart disease, respectively, whereas these occurred in none (0%) and one (0.4%) of 280 patients in the imatinib group, respectively.[22] These data are more striking at 6-year follow-up. Twenty-eight (10%) of 279 patients treated with nilotinib 300 mg twice per day, 44 (15.9%) of 277 patients treated with nilotinib 400 mg twice per day, and seven (2.5%) of 280 patients treated with imatinib 400 once per day had cardiovascular events. Cardiovascular events included ischemic heart disease, ischemic cerebrovascular disease, and peripheral artery disease, suggesting that the nilotinib-associated toxicity occurs in all arterial beds. Few venous events were

Table 1. Reports of Cardiovascular Toxicity in Patients Receiving Nilotinib

Author	Study Type	Patients	Cardiovascular End Point	Incidence
Le Coutre et al[56]	Retrospective, multi-institutional	N = 179; 84% treated on CT	PAD, lower limb, requiring intervention	11 of 179 patients (6.15%); angioplasty, n = 8; stent implantation, n = 8; amputation, n = 4
Aichberger et al[19]	Retrospective, single institution	N = 24; 25% treated on CT	PAD, lower limb, requiring intervention; myocardial infarction	4 of 24 (16.7%)
Quintás-Cardama et al[58]	Retrospective, single institution	N = 233; 100% treated on CT	Vascular events (deemed by oncologist as related to nilotinib): Raynaud's disease; CVA; peripheral vascular events; cardiac vascular events	5 of 233 (2.15%)
Larson et al[5]	ENESTnd trial, 3-year follow-up	N = 836; 100% treated on CT	PAOD, not defined; IHD, not defined	Imatinib: PAOD, 0 of 280 (0%); IHD, 1 of 280 (0.4%) Nilotinib 600 mg: PAOD, 5 of 279 (1.7%); IHD, 5 of 279 (1.8%) Nilotinib 800 mg: PAOD, 3 of 277 (1.1%); IHD, 6 of 277 (2.2%)
Larson et al[57]	ENESTnd trial, 6-year follow-up	N = 836; 100% treated on CT	Cardiovascular events; defined as ischemic heart disease, ischemic cerebrovascular disease, peripheral arterial disease	Imatinib: 7 of 280 (2.5%) Nilotinib 600 mg: 28 of 279 (10.0%) Nilotinib 800 mg: 44 of 277 (15.9%)
Levato et al[59]	Retrospective, single institution	N = 82	PAOD or other vascular occlusive event, not defined	Imatinib: 1 of 55 (1.8%) Nilotinib: 4 of 27 (14.8%)
Kim et al[60]	Prospective, multiple institutions	N = 159; approx. 50% treated on CT	Peripheral arterial disease, as assessed by ankle-brachial index	Imatinib (first line): 3 of 48 (6.3%) Nilotinib (first line): 7 of 27 (26%) Nilotinib (second line): 10 of 28 (35.7%)
Giles et al[20]	Meta-analysis from IRIS, TOPS, ENESTnd	N = 2,390; 100% treated on CT	PAOD, atherosclerotic and thrombotic events in accordance with ACC/AHA guidelines	No TKI: 3 of 533 (0.6%) Imatinib: 2 of 1,301 (0.2%) Nilotinib: 7 of 556 (1.3%)

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; approx., approximately; CT, clinical trial; CVA, cerebrovascular accident; ENESTnd, Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients; IHD, ischemic heart disease; IRIS, International Randomized Interferon Versus STI571 Study; PAD, peripheral arterial disease; PAOD, peripheral arterial occlusive disease; TKI, tyrosine kinase inhibitor; TOPS, Tyrosine Kinase Inhibitor Optimization and Selectivity.

seen in each arm. Importantly, the dose-dependent increased risk of events in the nilotinib arms implicates a drug-dependent process.[57]

A major shortcoming of these studies is the various definitions used for the cardiovascular end points. In one study, PAOD was defined as atherosclerotic and thrombotic events in the lower and upper extremities, consistent with a statement paper by the American College of Cardiology/American Heart Association, although the term PAOD itself is not typically used in cardiology.[61] However, PAOD events are not routinely recorded in oncology trials, which rely on Common Terminology Criteria for Adverse Events guidelines where definitions of peripheral arterial ischemia are vague (Appendix Tables A3 and A4, online only). In addition, if the underlying pathophysiology of nilotinib-associated PAOD is accelerated atherosclerosis, it represents a systemic condition affecting all vascular beds including coronary (cardiac) and cerebral vessels (as demonstrated by the results of the ENESTnd 6-year follow-up studies). In fact, the leading causes of death in atherosclerosis are cardiac ischemic and cerebral ischemic events, which were not considered in the meta-analysis of the IRIS, TOPS, and ENESTnd studies.[62] In this regard, an intriguing prospective study involving 159 patients on imatinib or nilotinib showed a higher incidence of abnormal ankle-brachial index (ABI) in patients on nilotinib (relative risk, 10.3). Abnormal ABI in patients treated with first- and second-line nilotinib was 26% and 35.7%, respectively, compared with 6.3% for first-line imatinib.[60] An abnormal ABI is a sensitive and specific test for PAD and implicates systemic atherosclerosis in arterial beds.[63]

As a result of the vascular and metabolic AEs of nilotinib, the toxicity profile of the drug label was amended to include vascular events. The European Medicines Agency recommended close cardiovascular monitoring for patients on nilotinib. Fasting blood lipids should be measured at baseline, at 3 and 6 months, and yearly thereafter; blood glucose should be assessed before treatment and then monitored as clinically indicated.[64] Indeed, if the nature of the vascular events in nilotinib is atherosclerosis, cardiovascular risk stratification and risk factor modification may be the most effective means of preventing cardiovascular events, and referral of high-risk patients treated on nilotinib to a cardiologist should be considered.

Bosutinib

Bosutinib is currently approved only for salvage therapy in CML. Unlike all other clinical BCR-ABL1 TKIs, bosutinib is inactive against KIT and PDGFR.[52] Nonhematologic toxicity is predominantly GI and hepatic and typically transient. Follow-up is shorter compared with other 2G TKIs, but available data suggest a relatively low incidence of cardiovascular AEs. At 24 months of follow-up of the Bosutinib Efficacy and Safety in Chronic Myeloid Leukemia (BELA) study in newly diagnosed patients, 10% of patients on bosutinib and 8% on imatinib had experienced cardiovascular events, including seven patients (3%) with grade 3 events and one patient (< 1%) with a grade 4 event. Cardiac failure occurred in one bosutinib-treated patient (< 1%) and two imatinib-treated patients (1%).[65] Although thus far the cardiovascular safety of bosutinib has been reassuring, long-term follow-up is needed.

Ponatinib

Ponatinib was designed to inhibit BCR-ABL1^{T315I} and was approved after encouraging results from a phase II study (Ponatinib Ph-Positive Acute Lymphoblastic Leukemia and CML Evaluation

Table 2. Univariable Analysis for Relative Risk of Serious Arterial Thrombotic Events With Ponatinib by Risk Category

Risk Category	Arterial SAE Rate in PACE Patients With Risk Category (%)	Arterial SAE Rate in PACE Patients, Excluding Patients With Risk Category (%)	Relative Risk (95% CI)
Age ≥ 65 years	19	11	1.8 (1.2 to 2.9)
History of ischemic cardiac disease	26	10	2.6 (1.6 to 4.0)
Diabetes mellitus	26	11	2.4 (1.5 to 3.8)
Arterial hypertension	20	6	3.2 (1.8 to 5.8)
Hypercholesterolemia	17	10	1.6 (1.0 to 2.7)
No. of cardiac risk factors + history of ischemic disease			
0	6	15	0.4 (0.1 to 1.0)
1	8	15	0.6 (0.3 to 1.1)
≥ 2	18	7	2.5 (1.4 to 4.5)

NOTE. Data adapted.[60]
Abbreviations: PACE, Ponatinib Ph-Positive Acute Lymphoblastic Leukemia and Chronic Myeloid Leukemia Evaluation; SAE, serious adverse event.

[PACE]).[8] In vitro profiling revealed potent inhibition of numerous tyrosine kinases including SRC, FGFR, PDGFR, and VEGFR1-3. The potency of ponatinib toward VEGFR2 is similar to that of TKIs designed to inhibit the VEGFR signaling pathway (VSP), such as sunitinib and sorafenib, which have been associated with hypertension and thrombosis (Fig 1).[66]

Cardiovascular toxicity. In the PACE study, with a median follow-up of 12 months, 6% of patients had cardiovascular AEs, 3% had cerebrovascular AEs, and 4% had peripheral AEs. At a median follow-up of 28 months, cumulative cardiovascular, cerebrovascular, peripheral AEs had increased to 10%, 7%, and 7%, respectively, with 14% arterial and an additional 3% venous serious AEs.[67] Twenty-six percent of patients developed hypertension, which was predictable given the VEGFR2 inhibition by ponatinib. Importantly, traditional atherosclerosis risk factors, such as age, hypertension, or diabetes, and especially ≥ two factors combined, predisposed patients to vascular serious AEs (Table 2). Interval analysis of the vascular toxicity at 24 months led to transient suspension of ponatinib marketing in the United States and a more restrictive label. The Evaluation of Ponatinib Versus Imatinib in CML (EPIC) trial, designed to test ponatinib as front-line treatment for CML, was closed after significant vascular toxicity was observed.

Post hoc analysis of combined ponatinib trial data established that ponatinib-associated cardiovascular toxicity is dose dependent and that older patients with history of diabetes or ischemic events are least tolerant of high dose-intensity.[68] Longer follow-up of the PACE study showed that most patients with BCR-ABL1^{T315I} had maintained cytogenetic responses despite dose reduction.[69] Dose optimization studies are planned to identify the optimal ponatinib dose that minimizes toxicity while maintaining efficacy. Whether it will be possible to identify a truly safe drug dose remains to be seen. Clearly, of all the BCR-ABL1 TKIs approved thus far, ponatinib has the most significant cardiovascular risk.

Although risks and benefits must be considered thoroughly before prescribing ponatinib, a subset of patients will undoubtedly benefit from the drug, particularly those with BCR-ABL1^{T315I}. Leukemia-related and cardiovascular risks must both be assessed, with good clinical judgment and appropriate counseling being critical for the decision process. The observation that pre-existing atherosclerosis predisposes to vascular AEs suggests that risk factor modification is warranted in patients being considered for ponatinib treatment. Interestingly, currently, the recommended initial dose is still 45 mg per day, although it seems good practice to reduce the dose when the desired response has been achieved.

POTENTIAL MECHANISMS UNDERLYING VASCULAR AEs

There are many unanswered questions regarding mechanisms of vascular AEs associated with nilotinib and ponatinib. Given the low incidence of vascular AEs with imatinib, it is likely that vascular toxicity is related to off-target rather than on-target effects. Ponatinib, for example, is a strong inhibitor of VEGFR1-3, which explains the high incidence of hypertension (similar to VSP inhibitors like sunitinib and sorafenib[70,71]). Specifically, VEGFR2 (KDR) inhibition with several TKIs has been associated with proteinuria and thrombotic microangiopathy.[66] However, it is unclear whether VSP inhibition is causally involved in vascular AEs; ponatinib inhibition of the angiopoietin receptor TIE-2 (KDR) and all FGFR kinases may enhance vascular toxicity.[72] In either case, identifying the specific kinases associated with toxicities could motivate re-engineering of compounds sparing the toxic kinases.[73] More elaborate clinical adjudication of ponatinib-associated vascular events will help guide mechanistic preclinical studies; at this point, it is unclear whether the arterial AEs on ponatinib represent thrombotic events, accelerated atherosclerosis, or some other vascular pathophysiology such as vasospasm.[74] If careful clinical adjudication suggested thrombosis, then further experiments testing the effects of ponatinib on platelets would be warranted. However, if the primary pathology were atherosclerosis, preclinical studies testing the effects of ponatinib on endothelial cell function would be helpful. In either case, more stringent clinical adjudication will help guide correlative basic studies.

Several studies have tested the effects of nilotinib or ponatinib on various cardiovascular cell types. One recent study showed that ponatinib, similar to other TKIs, inhibits platelet activation, spreading, granule function, and aggregation. The authors suggest that the vascular AEs with ponatinib may be a result of effects on other organs or cell types.[75] Preliminary studies suggest that nilotinib, in contrast to imatinib, has a detrimental effect on endothelial cell function in vitro.[76] More work is needed to better understand the effects of nilotinib or ponatinib in preclinical cardiovascular models. Specifying the

Table 3. Provisional Recommendations for Cardiovascular/Cardiometabolic Follow-Up of Patients Receiving BCR-ABL1 TKIs

Assessment	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Baseline	Follow good clinical practice				
Clinical cardiovascular assessment, including blood pressure		REC	REC	REC	REC
Fasting glucose		REC	ACI	ACI	REC
Fasting lipid panel		REC	ACI	ACI	REC
Echocardiogram		ACI	ACI*	ACI	ACI
ECG		REC†	REC	ACI	ACI
Ankle-brachial index		REC	ACI	ACI	REC
1-month follow-up					
Clinical cardiovascular assessment		REC	REC	ACI	REC
Blood pressure check		ACI	ACI	ACI	REC
3- to 6-month follow-up					
Clinical cardiovascular assessment		REC	REC	REC	REC
Blood pressure check		REC	ACI	ACI	REC
Fasting glucose		REC	ACI	ACI	ACI
Fasting lipid panel		REC	ACI	ACI	REC
Echocardiogram		ACI	ACI*	ACI	ACI
ECG		ACI†	ACI	ACI	ACI
Ankle-brachial index		REC	ACI	ACI	REC

NOTE. Practice guidelines regarding prevention of cardiovascular toxicity should be followed, including tobacco cessation counseling. In symptomatic patients or those with high cardiovascular risk, consider referral to cardiologist.
Abbreviations: ACI, as clinically indicated; ECG, electrocardiogram; REC, recommended; TKI, tyrosine kinase inhibitor.
*Low threshold for an echocardiogram in patient considered for treatment or being treated with dasatinib who has cardiopulmonary symptoms.
†ECG prior to starting, after 7 days after starting, and after each dose change (package insert).

type of vascular AE will also be critical for developing rational strategies for prevention and/or treatment. For example, in the case of arterial thrombosis, antiplatelet therapies may be beneficial, whereas statins may reduce the risk of atherosclerotic AEs. Screening tests should be incorporated prospectively to define the type of cardiovascular AEs. For example, ABI is a simple, sensitive, and specific means of diagnosing atherosclerotic PAD. Serum biomarkers and platelet studies may detect a prothrombotic state.

PRACTICAL CONSIDERATIONS

Managing Cardiovascular Risk

For most patients, TKIs have turned CML into a chronic disease. Given the high population frequency of cardiovascular disease and the increased frequency of vascular events with nilotinib and ponatinib, cardiovascular risk assessment and, if necessary, treatment need to be integrated into the management of patients with CML on TKIs. Table 3 lists provisional recommendations for assessment of cardiovascular risk factors at baseline and during follow-up. Patients at high risk of cardiac disease should be monitored carefully because ischemic cardiac events often occur as a result of accumulation of risk factors over time.[77,78] Prophylactic treatment with aspirin and statins represents a low-risk intervention in these groups of patients. In particular, extrapolating data from cardiology literature, if the primary etiology of vascular disease is thought to be systemic atherosclerosis, then statins may be the most effective means of preventing further vascular events. Because adding oral anticoagulants to antiplatelet therapy in patients with PAD failed to reduce cardiovascular events but increased severe bleeding risk, we do not recommend prophylactic anticoagulation.[79] Similarly, it would be difficult to justify a general recommendation for prophylactic antiplatelet therapy in low-risk patients, and such decisions need to be individualized. A more rational approach to prophylaxis will require a better understanding of the underlying pathophysiology.

Given the high risk of cardiovascular AEs with ponatinib, careful blood pressure monitoring at baseline and within days after starting therapy and aggressive management of ponatinib-associated hypertension are mandatory. Lowering the dose should be considered once the desired response has been attained. Whether it may be useful to monitor for proteinuria, similar to other TKIs with potent VEGF inhibition such as sunitinib, will have be determined in future studies.[66]

Patients considered high risk based on comorbidities or TKI selection may benefit from more frequent monitoring and from involvement of a cardiologist or a cardio-oncologist to optimize primary and secondary prevention. This is particularly relevant for the high-risk patients with CML in need of ponatinib who should be considered for referral to a specialized CML center with access to a cardio-oncology service to allow for optimal navigation between the Scylla of

Table 4. ABCDE Steps to Prevent Cardiovascular Disease in Patients With Chronic Myeloid Leukemia Treated With a Tyrosine Kinase Inhibitor

Step
A: Awareness of cardiovascular disease signs and symptoms
A: Aspirin (in select patients)
A: Ankle-brachial index measurement at baseline and follow-up to document peripheral arterial disease
B: Blood pressure control
C: Cigarette/tobacco cessation
C: Cholesterol (regular monitoring and treatment, if treatment indicated)
D: Diabetes mellitus (regular monitoring and treatment, if treatment indicated)
D: Diet and weight management
E: Exercise

TKI-resistant CML and the Charybdis of cardiovascular toxicity. In addition, a simple ABCDE algorithm is an established means to reduce cardiovascular events in the general population[80] and has already been recommended to prevent cardiovascular disease in survivors of breast cancer.[81] Applying a similar checklist to the patient with CML should be considered (Table 4).

Reporting Cardiovascular Events

The differing definitions used by the trial sponsor and the FDA to quantitate the high incidence of cardiovascular AEs in the PACE trial has drawn attention to a general problem with the reporting of cardiovascular toxicities in cancer trials. The National Cancer Institute Common Terminology Criteria for Adverse Events were developed to standardize reports of AEs in oncology trials. Unfortunately, the criteria used for cardiovascular events are vastly different from methodology used in cardiovascular drug trials and provide little information about the pathophysiology of AEs (Appendix Table A3). Moreover, cardiology clinical trials often include adjudication of reported AEs by an independent committee to provide more reliable safety data; however, this is not the current practice in oncology trials. Although oncology clinical trials require a causality assessment with respect to experimental drug, this is challenging in the case of cardiovascular AEs, which are common in the general population and tend to exhibit a chronic pattern. Participation of cardiologists in oncology clinical trial design and follow-up could help overcome some of the current shortcomings. Given these uncertainties, it remains critical for practicing oncologists to involve cardiologists or cardio-oncologists if a vascular AE is suspected. A more precise characterization of the event by a cardiovascular specialist (for example, an angiogram if an acute arterial thrombosis is suspected) will help guide treatment strategies. If the event is felt to be TKI associated, an alternative TKI needs to be considered. Drug selection must be individualized and will benefit from discussion between the cardiologist and oncologist.

CONSIDERATIONS FOR THE FUTURE

Although the success of TKIs in CML is still unique, there are indications that it may be repeated in other indolent hematologic malignancies. For instance, many patients with chronic lymphocytic leukemia treated with an inhibitor of Bruton's tyrosine kinase, ibrutinib, attain stable responses, but these are rarely complete and require continued maintenance.[82,83] Other cancers may follow, leading to a growing population of patients on long-term TKI therapy. This poses challenges to medical oncology, where for decades treatment paradigms were based on the extremes of either short-term curative or short-term palliative therapy, while effective but noncurative long-term therapies were unknown. These patient populations will require careful monitoring for late AEs over time spans that exceed the planned duration of most current clinical trials. A much deeper understanding of the causes of adverse effects will be needed to inform inhibitor design in a rational way, so that long-term toxicity can be minimized, while on-target activity is maintained or even improved.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Tyrosine Kinase Inhibitor–Associated Cardiovascular Toxicity in Chronic Myeloid Leukemia

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Expert Testimony: Bristol-Myers Squibb
Travel, Accommodations, Expenses: ARIAD, Bristol-Myers Squibb, Novartis, Pfizer

Acknowledgment

We thank Thomas O'Hare, PhD (University of Utah), and Thomas Force, MD (Vanderbilt University), for critically reading the article and Jenny Ottley (University of Utah) for administrative support.

Appendix

Table A1. Pharmacokinetics of Approved BCR-ABL1 Inhibitors

TKI and Dose	C_{max} (nM)	C_{trough} (nM)	C_{ave} (nM)*	PPB (%)†	Free C_{ave} (nM)‡	Naïve Shift (fold)	Effective C_{ave} (nM)§	Pharmacokinetics Reference
Imatinib 400 mg once a day	5,259	2,463	3,377	94	203	7.6	444	Peng B, et al: J Clin Oncol 22:935-942, 2004
Nilotinib 400 mg twice a day	3,599	1,699	2,754	98	55	21	131	Kantarjian et al[52]
Dasatinib100 mg once a day	172	8	27	96	1.1	2.4	11	Araujo JC, et al: Cancer 118:63-71, 2012
Bosutinib 500 mg once a day	377	198	287	95	14	1.8	159	Cortes JE, et al: Blood 118:4567-4576, 2011
Ponatinib				99.9		3.6		Cortes et al[9]
15 mg once a day	49	26	35		0.035		10	
30 mg once a day	121	56	84		0.084		23	
45 mg once a day	145	64	101		0.101		28	

NOTE. Data adapted from Schrock A, et al: Blood 122:3992, 2013 (abstr).
Abbreviations: C_{ave}, average concentration; C_{max}, maximum concentration; C_{trough}, trough concentration; PPB, plasma protein binding.
*Area under the curve corrected for 24-hour exposure.
†Data adapted from Kitagawa D, et al: Genes Cells 18:110-122, 2013.
‡Corrected for PPB.
§Corrected for human serum albumin/α_1-acid glycoprotein shift factor.

Table A2. Clinical Trials of Tyrosine Kinase Inhibitors in CML

Study Acronym	Full Study Name	Comparisons	Study Reference
IRIS	International Randomized Interferon Versus STI571 Study	Imatinib 400 mg per day *v* interferon alfa plus cytarabine	O'Brien et al[26]
TOPS	Tyrosine Kinase Inhibitor Optimization and Selectivity	Imatinib 400 mg per day *v* imatinib 400 mg twice per day	Cortes JE, et al: J Clin Oncol 28:424-430, 2010
DASISION	Dasatinib Versus Imatinib Study in Treatment-Naïve CML Patients	Dasatinib 100 mg per day *v* imatinib 400 mg per day	Kantarjian H, et al: N Engl J Med 362:2260-2270, 2010
ENESTnd	Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients	Nilotinib 300 mg twice per day *v* nilotinib 400 mg twice per day *v* imatinib 400 mg per day	Saglio et al[32]
BELA	Bosutinib Efficacy and Safety in CML	Bosutinib 500 mg per day *v* imatinib 400 mg per day	Cortes et al[7]
PACE	Ponatinib Ph-Positive ALL and CML Evaluation	Ponatinib 45 mg per day	Cortes et al[8]
EPIC	Evaluation of Ponatinib Versus Imatinib in CML	Ponatinib 45 mg per day *v* imatinib 400 mg per day	Lipton JH, et al: J Clin Oncol 32, 2014 (suppl 5S; abstr 7023)
CML IV	Tolerability-Adapted Imatinib 800 mg/d Versus 400 mg/d Versus 400 mg/d Plus Interferon Alfa in Newly Diagnosed CML	Imatinib 400 mg per day *v* imatinib 800 mg per day *v* imatinib 400 mg per day plus interferon	Hehlmann R, et al: J Clin Oncol 29:1634-1642, 2011
SPIRIT	STI571 (Imatinib) Prospective International Randomized Trial	Imatinib 400 mg per day *v* imatinib 400 mg per day plus cytarabine *v* imatinib 400 mg per day plus pegylated interferon *v* imatinib 600 mg per day	Preudhomme C, et al: N Engl J Med 363:2511-2521, 2010

Abbreviations: ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia.

Table A3. CTCAE Criteria for Peripheral Ischemia (disorder characterized by impaired circulation to an extremity)

CTCAE Grade for Peripheral Ischemia	Definition
1	—
2	Brief (< 24 hours) episode of ischemia managed nonsurgically and without permanent deficit
3	Recurring or prolonged (> 24 hours) and/or invasive intervention indicated
4	Life-threatening consequences; evidence of end-organ damage; urgent intervention indicated
5	Death

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

Table A4. Criteria Used by Cardiologists for PAD (abnormal ankle-brachial index < 0.9)

PAD Classification and Clinical Symptom	Rutherford Stage	Fontaine Stage
Asymptomatic	0	I
Intermittent claudication		
Mild claudication	1	IIa
Moderate claudication	2	IIb
Severe claudication	3	IIb
Critical limb ischemia		
Ischemic rest pain	4	III
Minor tissue loss	5	IV
Ulceration or gangrene	6	IV

NOTE. Data adapted from Kinlay S: Circulation 127:1241-1250, 2013.
Abbreviation: PAD, peripheral arterial disease.