Cardiovascular Adverse Events and Mitigation Strategies for Chronic Myeloid Leukemia Patients Receiving Tyrosine Kinase Inhibitor Therapy

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Cardiovascular (CV) risk mitigation is an important consideration in the management of chronic myeloid leukemia (CML) patients. Although BCR-ABL1 inhibition by tyrosine kinase inhibitors (TKI) has led to a significant improvement in prognosis, the majority of CML patients will require indefinite TKI therapy. Given the success of therapy, there has been a shift in focus to include CV care as part of routine patient management. To optimize outcomes, both patient-specific comorbidities and a detailed understanding of the cardiotoxicity safety profiles imparted by each TKI should be considered during agent selection. Clinicians face the challenge of early detection and management of these cardiotoxicities while balancing the risk-benefit ratios of maintaining life-saving cancer therapy. Advanced practitioners play a critical role in CML patient management that extends to the recognition and management of TKI-associated side effects. They should be cognizant of the potential for TKI-associated cardiotoxicities along with appropriate baseline risk assessments, active surveillance, and mitigation strategies as part of a collaborative team effort with cardio-oncologists.

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the Philadelphia (Ph) chromosome that results from the reciprocal translocation of the Abelson murine leukemia (*ABL1*) gene on chromosome 9 with the Breakpoint cluster gene (*BCR*) on chromosome 22 thereby producing a chimeric gene termed *BCR-ABL1* (Bartram et al., 1983; Groffen et al., 1984; Lugo et al., 1990; Rowley, 1973). BCR-ABL1 is a constitutively active protein tyrosine kinase that promotes leukemogenesis through modulation of key cellular signaling cascades (Franke et al., 1997; Ilaria

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& Van Etten, 1996; Notari et al., 2006; Salomoni et al., 1998). This aberrant signaling leads to alterations in transcriptional activity, enhanced proliferation, prolonged survival, and dysregulation of apoptosis.

Chronic myeloid leukemia represents 0.5% of all new leukemia cases with a median age at diagnosis of 65 years (Howlader et al., 2017). Approximately 8,450 cases of CML were diagnosed in 2020 with a rate of new cases at 1.9 per 100,000 men and women per year (Howlader et al., 2017). Imatinib mesylate (Gleevec; Novartis Pharmaceuticals, 2020a), nilotinib (Tasigna; Novartis Pharmaceuticals, 2020b), dasatinib (Sprycel; Bristol-Myers Squibb, 2018), ponatinib (Iclusig; Takeda Oncology, 2020), and bosutinib (Bosulif; Pfizer, 2019) are U.S. Food and Drug Administration (FDA)-approved TKIs utilized for the treatment of CML.

Inhibition of BCR-ABL1 by TKI therapy has significantly improved the long-term survival of patients (Bower et al., 2016; Jabbour & Kantarjian, 2018). Survival rates rose from 34% in 1995, prior to imatinib mesylate's approval in 2001, to 70% during 2010 to 2016, bringing CML patients within range of normal life expectancy for those responding to treatment (Bower et al., 2016; Howlader et al., 2017; Hughes & Ross, 2016). As such, the prevalence is expected to approach 180,000 by 2030 (Huang, Cortes, & Kantarjian, 2012). Despite this oncologic success, surmounting data have shown that TKIs are associated with a spectrum of cardiovascular adverse events (CVAE) that have led to a focus on CV risk prevention, active surveillance, and management strategies as emerging issues in the continuum of CML care.

A spectrum of CV-related toxicities ranging from chronic to life-threatening is reported to be higher for nilotinib, dasatinib, and ponatinib when compared with imatinib and bosutinib (Table 1). Accumulating evidence suggests that the occurrence of CVAEs is related to a combination of the patient's baseline CV risk factors and TKI-associated CV side effects, which may vary by type of off-target kinase inhibition. The CVAEs that have been associated with TKIs include cardiomyopathy, hypertension (HTN), arterial occlusive events (AOEs), venous thrombosis, QT interval prolongation, pulmonary arterial hypertension (PAH), and peripheral arterial occlusive disease (PAOD; Medeiros et al., 2018). There is no absolute contraindication to using any of the TKIs if the basis is comorbidities; however, the balance between efficacy for disease control and potential for CV toxicity is paramount to treatment selection.

This review will present current evidence supporting the indication of each TKI approved for CML treatment along with the CV safety profile. Management strategies for baseline CV assessment, active surveillance, and risk factor modification during treatment will be proposed for each TKI. Patient management should incorporate a multidisciplinary approach integrating cardiology and oncology expertise to evaluate and manage short- and long-term effects.

ON-TARGET VS. OFF-TARGET TOXICITY OF TKIs

A proposed mechanistic description of TKI-related CV side effects includes classification into "on-target" and "off-target" cardiotoxicity (Chen et al., 2008). On-target toxicity occurs when the TKI target in the cancer cell is present and has an important function in normal CV physiology (Chen et al., 2008; Force et al., 2007). This inhibition then leads to CV toxicity. An example of on-target toxicity is inhibition of platelet-derived growth factor receptors α and β (PDGFR). The development of these effects indicates clinically desirable and effective inhibition of the corresponding ligand-mediated receptor linked with oncogenesis (Shah et al., 2013). Off-target toxicity is observed when a nonselective TKI modulates the function of a kinase involved in normal vascular physiology and is not the target in cancer cells (Mouhayar et al., 2013). An example of this is ponatinib which, in addition to BCR-ABL1, also inhibits the vascular endothelial growth factor receptors (VEGFR) resulting in hypertension.

BCR-ABL1 INHIBITORS

Imatinib Mesylate

Imatinib mesylate was the first FDA-approved TKI for chronic phase (CP) CML in 2001 based on the International Randomized Study of Interferon and STI571 (IRIS) trial that randomly assigned 1,106 patients to receive imatinib mesyl-

Table 1. Cardiovascular Adverse Events Associated with TKIs Utilized for the Treatment of CML

Drug classification	Associated cardiotoxicity	Incidence (%)	Grade	AP considerations
Imatinib mesylate (Gleevec)	CHF and left ventricular dysfunction	0.7–1.1	3–4	• Baseline LVEF measurement (echo or MUGA) if history of severe CAD, MI, clinically significant arrhythmia, CHF, or symptomatic dyspnea • Monitor patients with cardiac disease/risk for cardiac failure or history of renal failure
	Arterial ischemic events	2	–	• Monitor peripheral pulses, color, skin temperature, and capillary refill
	Fluid retention resulting in pericardial effusion, pleural effusion, pulmonary edema, and ascites	2	1–2	• Monitor for increasing shortness of breath • Echo to monitor for increasing amount of pericardial effusion • Diuretics as needed
Nilotinib (Tasigna)	Fluid retention	3.9	3–4	• Diuretics as needed
	Ischemic heart disease	5–9	–	• ECG at baseline, 7 days after initiation, and repeated after dosing modifications • Manage cardiac risk factors
	Myocardial infarction	0.1–< 1	–	• CV risk assessment and modification prior to initiating therapy
	Hypertension	1–10	1–4	• Measure blood pressure at baseline and monitor during treatment
	Ischemic cerebrovascular events	1.4–3.2	–	• Perform neurological assessment if associated symptoms present during treatment (e.g., cognitive decline)
	PAOD	2.9–3.6	–	• Measure ankle-brachial index • Close cardiovascular monitoring • Fasting blood lipids should be measured at baseline, at 3 and 6 months, and yearly thereafter • Cardiovascular risk stratification and risk factor modification • Referral of high-risk patients to cardiologist
	Prolonged QT interval	< 1–10	–	• Ongoing monitoring and correction of serum potassium and magnesium. • Avoid concomitant QT prolonging medications • Hold if QTc prolongation > 480 ms or a change from baseline of > 60 ms
	Arterial vascular occlusive events, median time to onset 60 mo	9.3–15.2	–	• Cardiovascular risk stratification and risk factor modification • Referral of high-risk patients to cardiologist
	Hyperglycemia	36	–	• Monitor blood glucose
	Hyperlipidemia: increase in total LDL, and HDL within 12 mo of treatment.	48–88	–	• Measure fasting blood lipids at baseline, at 3 and 6 months, and yearly thereafter

Note. CHF = congestive heart failure; LVEF = left ventricular ejection fraction; echo = echocardiogram; MUGA = multigated acquisition scan; CAD = coronary artery disease; MI = myocardial infarction; ECG = electrocardiogram; CV = cardiovascular; POAD = peripheral arterial occlusive disease; TIA = transient ischemic attack; CVA = cerebrovascular accident. Information from Aichberger et al. (2011); Bristol-Myers Squibb (2018); Kim et al. (2013); Novartis Pharmaceuticals (2020a, 2020b); Pfizer (2019); Rea et al. (2014); Takeda Oncology (2020); Xu et al. (2009).

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Table 1. Cardiovascular Adverse Events Associated with TKIs Utilized for the Treatment of CML (cont.)

Drug classification	Associated cardiotoxicity	Incidence (%)	Grade	AP considerations
Dasatinib (Sprycel)	Fluid retention	5	3–4	• Diuretics as needed
	Localized edema, superficial	14	1–4	• Elevate affected limb(s) • Low sodium diet
	Cardiac ischemic events	3.9	3–4	• Evaluate for signs and symptoms of cardiopulmonary disease throughout treatment
	Conduction system abnormalities	7	–	• Baseline ECG • Monitor PR interval for heart blocks
	Transient ischemic attack	0.8	3–4	• Monitor for signs and symptoms of TIA/CVA
	Congestive heart failure	2–4	1–4	• Baseline echo with Doppler studies for high-risk patients prior to starting if any cardiopulmonary symptoms
	Prolonged QT interval	1	–	• Monitor patients with pre-existing congenital long QT syndrome or receiving an anti-arrhythmic, QT prolonging medications • Monitor electrolytes (K, Mg)
	Pulmonary arterial hypertension	5	1–4	• Monitor for increasing shortness of breath • Monitor echocardiogram for increasing right ventricular systolic pressure
	Arterial ischemic events	5	–	• Baseline LVEF measurement (echo or MUGA) • Monitor extremities for peripheral pulses, color, temperature, and capillary refill
Bosutinib (Bosulif)	Heart failure	1.5–5.3	–	• Baseline LVEF measurement (echo or MUGA) • Monitor for signs and symptoms of heart failure (e.g., shortness of breath, lower extremity edema, increased abdominal girth)
	Pericardial effusion	0.4–< 10	–	• Monitor for increasing shortness of breath, and development of cardiac tamponade • Echo to evaluate size and location of pericardial fluid
	Prolonged QT interval	< 10	–	• Baseline ECG • Monitor QT interval during therapy • Avoid concomitant administration of QT prolonging drugs

ate or interferon alfa plus low-dose cytarabine (O'Brien et al., 2003). After a median follow up of 18 months, imatinib mesylate showed a superior rate of complete cytogenetic response (CCyR; normal karyotype by bone marrow analysis; 76% vs. 14%), tolerability profile, and lower likelihood of progression to accelerated or blast crisis phase as compared with interferon alfa plus low-dose cytarabine, respectively (O'Brien et al., 2003). Grade 3 to 4 fluid retention, including pericardial effusions, was reported in 2% of patients on imatinib mesylate. After nearly 11 years of follow up for IRIS, serious CVAEs are rarely found in CML patients receiving imatinib mesylate, at 7.1% (n = 39/551; Hochhaus et al., 2016).

Despite an initial report that imatinib mesylate generated a signal for congestive heart failure (CHF) and left ventricular contractile dysfunction, several subsequent studies have not demonstrated a high incidence for cardiomyopathy (Kerkelä et al., 2006; Wolf et al., 2010). Long-term follow up of patients receiving imatinib mesylate has not shown an increased risk for CVAEs when compared with the newer second-generation (nilotinib, dasatinib) and third-generation (ponatinib) TKIs (Cortes et al., 2012a, 2018a; Hochhaus et al.,

Table 1. Cardiovascular Adverse Events Associated with TKIs Utilized for the Treatment of CML (cont.)

Drug classification	Associated cardiotoxicity	Incidence (%)	Grade	AP considerations
Ponatinib (Iclusig)	Hypertension	42–53	1–4	• Monitor blood pressure regularly
	Arterial occlusive events (arterial thrombosis, ischemic stroke, and ischemic cerebral infarction)	13–31	1–4	• CV risk assessment and modification prior to therapy • Antiplatelet therapies may be warranted • Statins may reduce the risk of atherosclerotic AEs
	Atrial fibrillation	7	–	• Anticoagulation to prevent stroke
	Cardiac dysrhythmias	19	–	• Baseline ECG, and continuous monitoring during therapy • Maintain electrolytes (K, Mg) within normal limits
	Heart failure	7	3–4	• Baseline LVEF measurement (echo or MUGA) • Monitor for signs and symptoms of heart failure (e.g., shortness of breath, lower extremity edema, increased abdominal girth)
	Myocardial infarction	2	3–4	• CV risk assessment and modification prior to initiating therapy
	PAOD, median time to onset of 2 years	12	–	• Measure ankle-brachial index • Close cardiovascular monitoring • Fasting blood lipids should be measured at baseline, at 3 and 6 months, and yearly thereafter • Cardiovascular risk stratification and risk factor modification • Referral of high-risk patients to cardiologist

Note. CHF = congestive heart failure; LVEF = left ventricular ejection fraction; echo = echocardiogram; MUGA = multigated acquisition scan; CAD = coronary artery disease; MI = myocardial infarction; ECG = electrocardiogram; CV = cardiovascular; POAD = peripheral arterial occlusive disease; TIA = transient ischemic attack; CVA = cerebrovascular accident. Information from Aichberger et al. (2011); Bristol-Myers Squibb (2018); Kim et al. (2013); Novartis Pharmaceuticals (2020a, 2020b); Pfizer (2019); Rea et al. (2014); Takeda Oncology (2020); Xu et al. (2009).

2016; Kantarjian et al., 2006). Interestingly, some studies suggest that imatinib mesylate may impart a beneficial CV effect (Frost et al., 2015; Pouwer et al., 2018). In animal models, imatinib mesylate decreased plasma cholesterol and atherosclerotic lesion area leading to increased plaque stability (Pouwer et al., 2018). Moreover, it also improved exercise capacity among PAH patients after inadequate response to prior therapies (Frost et al., 2015). These findings suggest that imatinib mesylate may provide a cardioprotective effect; however, further studies elucidating these mechanisms are needed.

Although CV toxicities are rare with imatinib mesylate, ongoing cardiac assessment should become an integral part of care. Patients with preexisting cardiac risk factors should be actively monitored and treated accordingly. Edema of any grade occurs in 55% of patients, which can have cardiac implications in patients with underlying CHF (O'Brien et al., 2003). Patients should be educated on the signs and symptoms of fluid retention.

Dasatinib

Dasatinib is a highly potent dual Src/Abl inhibitor that is 325-fold more potent at inhibiting BCR-ABL1 than imatinib mesylate with efficacy in overcoming specific mutations in the BCR-ABL1 kinase that confer imatinib mesylate resistance (Hochhaus et al., 2008; O'Hare et al., 2005). This second-generation TKI was initially approved in 2010 for CML patients who were imatinib mesylate resistant or intolerant before gaining front-line approval based on the Dasatinib Versus Imatinib Study in Treatment-Naive CML Patients (DASISION) trial (Kantarjian et al., 2010; Talpaz et al., 2006). The DASISION trial randomized 519 newly diagnosed CP CML patients to receive dasatinib 100 mg once

daily or imatinib mesylate 400 mg once day. Higher and earlier rates of CCyR (77% vs. 66%) and major molecular response (MMR; 46% vs. 28%) were observed with dasatinib as compared with imatinib mesylate, respectively. Achievements of early cytogenetic and molecular responses correlate with both improved progression-free survival and overall survival (Cortes et al., 2014, 2016a).

Both PAH and QT prolongation are two potential cardiac safety signals that have been associated with dasatinib, carrying a median onset time of 34 months for a PAH diagnosis (Kantarjian et al., 2010; Mattei et al., 2009; Montani et al., 2014; Shah et al., 2014). In 2009, an initial published case of PAH was reported in an allogeneic hematopoietic transplant CML patient with spontaneous improvement following dasatinib discontinuation (Mattei et al., 2009). Subsequently, nine cases of dasatinib-induced PAH were identified in a French Registry between November 2006 to September 2010 ranging from moderate to severe cases (Montani et al., 2012). Dasatinib discontinuation led to improvement without complete resolution by 4 months, suggesting PAH may be partly reversible. After 5 years of follow-up in DASISION, PAH was reported in 5% of patients, with 9 of the 14 patients having a concurrent pleural effusion (Cortes et al., 2016b). Only one of these patients underwent a right heart catheterization, which did not confirm PAH. Right heart catheterization is necessary in order to establish a diagnosis of PAH (Hoeper et al., 2013).

Symptoms of PAH may be nonspecific such as dyspnea or edema. A chest x-ray is recommended for initial evaluation of dyspnea, as dasatinib-related pleural effusions occur in approximately 28% of patients, with a higher incidence in those ≥ 65 years old (Cortes et al., 2016b). The mechanism of pleural effusions may involve off-target inhibition of PDGFRβ (Brixey & Light, 2010). In another study of 662 CP CML dasatinib-treated patients who were imatinib mesylate resistant or intolerant, only two cases of PAH were reported after a median follow-up of 6 years with no cases of QT prolongation (Shah et al., 2014). However, no right-heart cardiac catheterization was performed. Clinical findings and history warrant referral to a cardio-oncologist for PAH management with discontinuation of dasatinib upon confirmed diagnosis.

The US prescribing information for dasatinib reports only 1% of 2,440 patients experienced relevant QTc prolongation (QT > 500 ms) across all doses tested in clinical trials (Bristol-Myers Squibb, 2018). Patients with risk factors for QT prolongation such as hypokalemia or hypomagnesemia, concomitant antiarrhythmic medications, or other medications known to prolong QT interval may be at increased risk. Risk vs. benefit should be considered for the utilization of dasatinib in patients ≥ 65 years of age with underlying cardiopulmonary conditions such as chronic obstructive pulmonary disease, asthma, or CHF.

Nilotinib

Nilotinib is a second-generation TKI that was developed for the ability to overcome imatinib mesylate–resistant *BCR-ABL1* mutations before obtaining front-line approval in 2007 based on the Evaluating Nilotinib Efficacy and Safety in Clinical Trials Newly Diagnosed Patients (ENESTnd) trial (Hochhaus et al., 2016; Weisberg et al., 2006). Deeper and earlier rates of molecular response and lower rates of progression to advanced phases were reported for nilotinib as compared with imatinib mesylate (Hochhaus et al., 2016; Hughes et al., 2019).

Similar to dasatinib, evidence for QT prolongation was found during a review of 2,200 screening electrocardiograms (ECGs) from 119 patients receiving second-line nilotinib (Kantarjian et al., 2006). These data prompted a black box warning for nilotinib, although the ENESTnd 5-year update did not show a significant difference in QT prolongation for nilotinib when compared with imatinib mesylate (Hochhaus et al., 2016). An ECG to assess the QT interval is advised at baseline and 7 days after commencing nilotinib at dosing adjustments or interruptions, then as clinically warranted (Novartis Pharmaceuticals, 2020b). Appropriate management should include an assessment for the risk of QT prolongation based on medical history and concomitant medications known to prolong QT such as certain antiarrhythmics, antifungals, antibiotics, tricyclic antidepressants, and cytochrome P450 3A4 (CYP3A4) inhibitors. Hypokalemia and hypomagnesemia require correction before starting therapy. Fasting requirements to avoid food at least 2 hours before

and 1 hour after taking nilotinib are necessary as non-fasting may result in increased absorption leading to QT prolongation.

In 2011, a report by Aichberger and colleagues reported PAOD in a subset of patients receiving nilotinib. Peripheral arterial occlusive disease is a systemic disease caused by atherosclerosis that can lead to the occlusion or stenosis of arteries in the limbs (Hirsch et al., 2001). Patients may present with symptoms of claudication, leg numbness or weakness, thinning of skin on lower legs, or non-healing skin ulcers. Another retrospective study on nilotinib identified PAOD in 6.15% of patients (N = 179) that affected the lower limbs (Le Coutre et al., 2011). Nine of these cases involved the femoral superficial artery necessitating angioplasty, with eight patients requiring stent placement and four receiving amputation. Subsequent multicenter series have also shown a higher incidence of PAOD ranging from 2% to 14.8% in small cohorts of front- and second-line nilotinib-treated patients (Giles et al., 2013; Levato et al., 2013; Quintas-Cardama et al., 2012). The majority of these patients had baseline risk factors for PAOD, including diabetes mellitus (DM), nicotine abuse, dyslipidemia, obesity, hypertension, and age ≥ 60 years old, suggesting nilotinib may exacerbate preexisting arteriosclerotic conditions (Aichberger et al., 2011; Giles et al., 2013; Le Coutre et al., 2011; Levato et al., 2013; Quintas-Cardama et al., 2012). Early PAOD has been identified more frequently using the ankle-branchial index (ABI), suggesting this method may be utilized in conjunction with ongoing CV assessment and mitigation strategies to assess for PAOD in patients receiving nilotinib (Hsu et al., 2013).

The ENESTnd data showed a higher cumulative incidence of CVAEs, including elevations in total blood cholesterol (27% vs. 3.9%) and glucose elevations (49% vs. 30%) of any grade for nilotinib than imatinib mesylate, respectively, after a minimum follow-up of 5 years (Hochhaus et al., 2016). Hypercholesterolemia was more frequent during the initial year on nilotinib with decline following initiation of a statin. Ischemic heart disease (3.9% vs. 1.8%), ischemic cerebrovascular event (1.4% vs. 0.4%), and PAOD (2.5% vs. 0%) were also greater for nilotinib. Baseline Framingham Risk Scores (FRS) for CV risk was predictive for risk of CVAE development; therefore, a baseline assessment should be established. The 10-year update of ENESTnd reports that while CVAEs are more frequent for nilotinib as compared with imatinib mesylate, the frequency of CVAEs continued to occur at similar rates as at 5 years (Hughes et al., 2019).

Ponatinib

The pivotal Ponatinib Ph+ acute lymphoblastic leukemia (ALL) and CML Evaluation (PACE) trial evaluated the safety and efficacy of ponatinib in patients with resistance or intolerance to dasatinib or nilotinib or harboring *BCR-ABL1*^{T315I} (Cortes et al., 2013). The T315I mutation may be present in up to 20% of patients, conferring resistance to all FDA-approved TKIs except ponatinib (Druker et al., 2001; Gorre et al., 2001). Ponatinib demonstrated robust clinical activity with significant and durable responses in these heavily pretreated populations after 15 months of follow-up (Cortes et al., 2012b). These data led to the accelerated approval of ponatinib in 2012.

Interim data analysis showed that venous thromboembolic events (not reported vs. 5%) and arterial occlusive events (AOEs) composed of cardiovascular (9% vs. 7%), cerebrovascular (6% vs. 3%), and peripheral vascular events (6% vs. 5%) were slightly higher after 24 months vs. 15 months of follow-up, respectively (Cortes et al., 2013; Kantarjian et al., 2014). Subsequently, in October 2013 the FDA transiently withdrew ponatinib from the market after the real-world incidence of serious arterial thrombotic events was reportedly higher than the label disclosed. Investigators for ongoing clinical trials implemented dose reductions based on protocol- and response-defined criteria in an effort to mitigate these risks. Recognizing there was no alternative TKI for patients otherwise responding to ponatinib, the FDA reintroduced ponatinib in January 2014 with an updated label to include a boxed warning for the risk of arterial thrombotic events (Takeda Oncology, 2020). Ponatinib is limited to the treatment of adult patients with CML or Ph+ ALL harboring T315I or adult patients with CML or Ph+ ALL in whom no other TKI is indicated. Subsequently, the EPIC (Evaluation of Ponatinib vs. Imatinib in CML) trial for newly diagnosed CP CML was discontinued

due to a higher incidence of AOEs for the ponatinib arm (7%) than the imatinib arm (2%; Lipton et al., 2014). Ponatinib is not recommended in the front-line setting for newly diagnosed CML.

Retrospective analysis of PACE revealed the AOEs were dose dependent and predominantly in patients with baseline risk factors such as 55% having a history of ischemic heart disease and 95% having one or more risk factors with or without a history of ischemic disease such as HTN, DM, hypercholesterolemia, or obesity. This causal relationship between dose dependence and the increased risk for toxicities has prompted investigations into optimizing dosing to improve patient outcomes. Data from both the phase I and PACE trials showed meaningful responses in heavily pretreated CML patients at ponatinib dosages lower than the approved 45 mg per day dose (Cortes et al., 2012b; Hochhaus et al., 2014). After 5 years of PACE trial follow-up, more than 90% of chronic phase CML patients achieving a major cytogenetic response (MCyR) or MMR had maintained their response at 40 months following dose reduction (Cortes et al., 2018a). The cumulative incidence of AOEs increased in time to 31% with a median time to onset of 13 months, whereas the exposure-adjusted incidence of new AOEs remained stable. Collectively, these results suggest the 45-mg once daily dosing may not be optimal in balancing CV risks with efficacy as lower dose levels may provide a meaningful response.

Further support for dose-dependent optimization stems from a multivariate analysis of 683 patients enrolled in the phase I PACE and EPIC trials showing a significant association between ponatinib dose intensity and risk for certain vascular adverse events (Dorer et al., 2016). Based on this analysis, each 15-mg per day dose reduction is predicted to result in a 33% reduction in the risk for an AOE. History of ischemic disease, elderly age, and dose intensity were the strongest independent prognostic predictors for the risk of an AOE. These observations have led to randomized clinical trials testing lower doses of ponatinib in an effort to minimize toxicities (Lipton et al., 2016). Knowledge of the CV risks attributable to ponatinib is paramount to the evaluation and management of CML patients. Throughout ponatinib therapy, these patients should be co-managed with a cardio-oncologist independent of whether there is a history of CV disease to mitigate the potential for toxicities.

Bosutinib

Bosutinib is a second-generation TKI that earned expanded approval in 2017 to include newly diagnosed CML patients based on the Bosutinib Trial in First-Line Chronic Myeloid Leukemia Treatment (BFORE) after showing higher rates of MMR compared with imatinib mesylate at 12 months (Cortes et al., 2018b). Prior approval in 2012 was based on significant activity in CML patients who were either resistant or intolerant to prior therapy in the Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia (BELA) trial (Cortes et al., 2012a). Interim analysis from BELA suggests there are no increased risks of CV events after 4 years of follow-up (Gambacorti-Passerini et al., 2012). Likewise, the BFORE data show similar low rates of cardiac and peripheral vascular events for bosutinib (3% and 1.5%) and imatinib mesylate (0.4% and 1.1%), respectively (Cortes et al., 2018b). A retrospective analysis evaluating two studies on bosutinib-receiving CML patients, a phase I/II (N = 570) of second-line or higher and those resistant or intolerant to prior TKIs, and a phase III of first-line bosutinib (N = 248) vs. imatinib mesylate (N = 251), shows the incidences of cardiac and vascular events were similar to imatinib at ≥ 48 months of follow-up (Cortes et al., 2016b). A history of hyperlipidemia or hypercholesterolemia, vascular disease, and performance status > 0 were prognostic for such events in relapsed or refractory patients whereas older age and history of DM were prognostic in newly diagnosed patients. Collectively, these results suggest that bosutinib has a lower incidence of CV toxicities as compared with other second- and third-generation TKIs. While these incidences are low, longer-term follow-up is needed to further extrapolate any differences. Patients receiving bosutinib should have active monitoring for potential cardiotoxicities as part of standard of care.

MANAGEMENT OF CV DISEASE IN CML PATIENTS

Given the excess risk of CVAEs in CML patients and the challenges that these patients face in can-

cer treatment after a CV event, careful CV risk stratification and surveillance should be an essential part of management. Surmounting evidence is showing that CML patients with preexisting CV risk factors are at an increased risk for CVAEs (Hoffmann et al., 2015). Aggressive management of modifiable risk factors and CV surveillance during treatment based on the specific risk profile of each TKI is advised. Based on available data, there are several expert recommendations on CV surveillance in CML patients receiving TKIs (Breccia et al., 2016, 2017; Li et al., 2015). Cardio-oncology care should include guideline-directed principles (Hunt et al., 2005; Ponikowski et al., 2016; Yancy et al., 2016) of diagnosis, prevention, and treatment with particular attention toward individual patient clinical profiles including age, gender, pre-existing CV risk factors, and TKI. Particularly in "high-risk" patients, aggressive risk factor modification and ongoing monitoring of CV complications is crucial to optimize primary or secondary prevention.

Patients are considered at increased risk for developing CVAEs if they have the following criteria: Older age (> 60 years), two or more CV risk factors (smoking, HTN, DM, hyperlipidemia, active tobacco use, and obesity), prior cardiotoxic chemotherapy or mediastinal irradiation, and compromised cardiac function (left ventricular ejection fraction < 55%), more than moderate valvular heart disease, or coronary artery disease. 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 (Moslehi, 2013; Yusuf et al., 2004).

The "ABCDE" Approach to CV Management in CML During TKI Treatment

The ABCDE schematic was initially developed at Johns Hopkins Hospital to minimize the risk of heart disease in all patients as part of the Million Hearts Initiative for guiding a consistent, comprehensive approach to managing CV risk in daily clinical practice (Hsu et al., 2013). The ABCDE approach was later adapted in cardio-oncology to prevent heart disease in breast cancer (Montazeri et al., 2014), prostate cancer (Bhatia et al., 2016), and CML (Barber et al., 2017). A proposed algorithm for the management of cardiovascular disease (CVD) in patients with CML receiving TKI therapy is summarized below.

"A" is for Awareness, Assessment, Aspirin, Anticoagulation, and Ankle-Brachial Index Measurement

Awareness. The first step in the assessment of the risk for cardiotoxicity is identification and treatment of coronary heart disease (CHD) or a CHD risk equivalent. The CHD risk equivalent includes individuals with noncoronary atherosclerotic vascular disease (cerebrovascular disease, PAOD, or abdominal aortic aneurysms), DM, chronic kidney disease (CKD), and risk factors that include tobacco use, HTN, dyslipidemia, increasing age, a family history of premature CHD, obesity, and lack of brisk exercise (Hsu et al., 2013).

Assessment. The FRS remains the most commonly used global risk assessment tool to estimate the total CVD risk and lifetime risk for all CVD events, including CHD, stroke, PAOD, and heart failure (National Heart, Lung, and Blood Institute, 2013).

Aspirin. Substantial evidence supports the use of aspirin in the primary and secondary prevention of CVD (Antithrombotic Trialists' Collboration, 2002; Antithrombotic Trialists' Collboration et al., 2009). A low-dose aspirin (75–100 mg/d) when compared with high-dose aspirin (325 mg/d) has no significant difference in the primary endpoint of CV death, myocardial infarction (MI), or stroke, based on the findings from the Clopidogrel optimal loading dose Usage to Reduce Recurrent Events-Organization to Assess Strategies in Ischemic Syndromes (CURRENT OASIS 7) trial (Investigators et al., 2010).

Anticoagulation. Dual antiplatelet therapy (DAPT) with clopidogrel and aspirin has been shown to reduce adverse outcomes, including death, nonfatal MI, and stroke in patients after both non–ST-elevation acute coronary syndrome as well as ST-elevation MI in the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial (Yusuf et al., 2001), the Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction (CLARITY-TIMI28) trial (Sabatine et al., 2005), and the Clopidogrel and Metoprolol in Myocardial Infarction trial (COMMIT/CCS2; Chen et al., 2005). Current guidelines

recommend DAPT for at least 12 months in individuals after acute coronary syndrome (ACS) or after drug-eluting stents (Levine et al., 2011).

Ankle-Brachial Index. For patients who will receive a TKI associated with an increased risk for CVAEs, especially PAOD, routine ABI can be considered before starting a TKI. The new guideline on the management of PAOD (Gerhard-Herman et al., 2017) in the general population recommends (class IIa) routine ABI for patients at increased risk of PAOD, including (1) age ≥ 65 years, (2) age 50–64 years with risk factors for atherosclerosis, and (3) age < 50 years with DM and one additional risk factor, or (4) patients with atherosclerotic disease in another vascular bed. Surveillance ABI for patients who are receiving ponatinib or nilotinib has been recommended by experts, but evidence is lacking for this recommendation. European LeukemiaNet recommends surveillance ABI (or duplex ultrasonography) every 6 to 12 months in patients on ponatinib or nilotinib (Steegmann et al., 2016).

"B" is for Blood Pressure

Elevated blood pressure (BP) is a common side effect associated with the VEGF signaling pathway (VSP) inhibitor TKIs, such as ponatinib. Hypertension is an important risk factor for CHD as well as stroke, atrial fibrillation, CHF, left ventricular hypertrophy, renal failure, and dementia (Rosendorff et al., 2007). New-onset or worsening HTN that is associated with TKIs can develop early (within 24 h) after initiation, but typically is observed within the first few weeks of therapy (Maitland et al., 2009). Guidelines by the Joint National Committee (JNC8) support treatment of BP once the systolic BP is > 140 mm Hg or the diastolic BP is > 90 mm Hg (Armstrong & Joint National, 2014). Current guidelines suggest a lower target of 130/80 mm Hg in patients with DM, CKD, or CHD. Aggressive BP targets endorsed in the recent AHA/ACC BP guidelines should be considered in cancer survivors, especially those with compromised left ventricular function or patients on VSP inhibitors (Whelton et al., 2018).

"C" is for Cholesterol and Cigarette/Tobacco Cessation

Cholesterol. Elevated cholesterol is associated with increased CV risk (Kannel et al., 1961; Neaton & Wentworth, 1992); lipid-lowering medications can reduce this risk. Management of cholesterol is defined by the National Cholesterol Education Program (NCEP) guidelines (Grundy et al., 2019). Patients are stratified into low (0–1 risk factor), moderate (≥ 2 risk factors but FRS < 10%), moderately high (≥ 2 risk factors and FRS 10%–20%), and high-risk groups (CHD, CHD risk equivalent, or FRS > 20%). Cardiovascular disease risk algorithms are published for patients with certain site-specific cancers, including childhood cancer survivors (Chow et al., 2015, 2018). If statin therapy is recommended, a review of existing medications is needed to avoid potential drug-drug interactions.

Cigarette/Tobacco Cessation. Tobacco use in all forms is proatherogenic and prothrombotic. A meta-analysis of 20 prospective cohort studies demonstrated a 36% relative reduction in mortality for CHD patients who were able to quit smoking (Critchley & Capewell, 2003). Smoking cessation should be encouraged; however, if unsuccessful, clinicians should discuss treatment strategies and resources including behavioral counseling, telephone resources (e.g., 1-800-QUIT-NOW), and consider referral to a nicotine cessation clinic or program within a cancer center or designated program within the institution.

"D" is for Diabetes, Diet, and Weight Management

Diabetes. Diabetes mellitus and pre-DM are important risk factors for CHD. The American Diabetic Association (ADA) recommends screening for any adults who are overweight or obese, or beginning at age 45 years. If the patient has DM, determine the presence of complications such as autonomic or peripheral neuropathy, retinopathy, orthostatic hypotension, CKD, or PAOD. Next, determine whether the patient experiences symptoms related to DM complications or if episodes of hypoglycemia or hyperglycemia occur. Consider referral to a dietitian for medical nutrition therapy and set a hemoglobin A1c goal of ≤ 7%. Recognize TKI agents, such as nilotinib, that impair glucose metabolism, and therapeutic exposures that increase the risk of DM (Meacham et al., 2009; Moslehi, 2016; Saylor & Smith, 2009).

Refer cancer patients with DM to a certified DM educator and registered dietitian if needed.

Diet and Weight Management. Obesity (BMI ≥ 30 kg/m^2) is a major risk factor for developing CHD, HTN, impaired glucose tolerance, obstructive sleep apnea (which itself is strongly associated with CHD), and dyslipidemia.

"E" is for Exercise, Electrocardiogram, and Echocardiogram

Exercise. Physical activity has many benefits, including weight loss, lipid control, BP improvement, and insulin sensitization. There is reasonable evidence to support the conclusion that exercise improves cardiorespiratory function after the completion of cancer therapy. Cardiorespiratory function is associated with a higher incidence of short- and long-term treatment-related toxicities (e.g., CVD), higher symptom burden (e.g., fatigue), and increased risk of all-cause and cancer-specific mortality in patients with cancer (Courneya et al., 2009; Jones et al., 2012; Lakoski et al., 2015).

Echocardiogram. Currently, there is no evidence-based recommendation for routine echocardiogram in CML patients receiving TKIs; however, a low threshold for performing them in patients with cardiopulmonary symptoms is warranted (Moslehi & Deininger, 2015). Echocardiogram with Doppler studies would provide a noninvasive assessment and estimation of pulmonary artery pressure before starting dasatinib if there is concern for PAH. The European Society of Cardiology recommends an echocardiogram every 3 months while patients are receiving dasatinib; however, there are no data to support an optimal time interval between them (Zamorano et al., 2016).

IMPLICATIONS FOR ADVANCED PRACTITIONERS

The treatment success and improved survival outcomes in CML patients greatly depends on optimal selection and judicious use of the available TKIs, since many patients will require indefinite treatment with potential for sequential treatment due to inadequate response or intolerance. Cardiovascular risk mitigation and monitoring should become part of clinical practice in CML patient care algorithms. Advanced practitioners are in a pivotal position prior to and throughout TKI therapy to educate patients, monitor, and manage toxicities. We should utilize a multidisciplinary approach including cardio-oncology to manage the CV adverse effects. Thus, advanced practitioners caring for CML patients should be cognizant of the spectrum of TKI-associated CV complications along with the incorporation of appropriate risk mitigation strategies into routine clinical practice. ●

Disclosure

Dr. Nodzon has served as a consultant for Takeda, AbbVie, and Genentech, and as a speaker for AbbVie and Genentech. Dr. Fadol and Dr. Tinsley have no conflicts of interest to disclose.

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