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CARDIO-ONCOLOGY (LA BALDASSARRE, SECTION EDITOR)

Cardiovascular Toxicities Associated with Tyrosine Kinase Inhibitors

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Abstract

Purpose of Review To provide a detailed overview of cardiovascular adverse events associated with the use of tyrosine kinase inhibitors across different tumor types.

Recent Findings Despite an undeniable survival advantage of tyrosine kinase inhibitors (TKIs) in patients with hematologic or solid malignancies, the accompanying off-target cardiovascular adverse events can be life-threatening. In patients with B cell malignancies, the use of Bruton tyrosine kinase inhibitors has been associated with atrial and ventricular arrhythmias, as well as hypertension. Cardiovascular toxic profiles are heterogeneous among the several approved breakpoint cluster region (BCR)-ABL TKIS. Notably, imatinib might be cardioprotective. Vascular endothelial growth factor TKIs, constituting the central axis in the treatment of several solid tumors, including renal cell carcinoma and hepatocellular carcinoma, have strongly been associated with hypertension and arterial ischemic events. Epidermal growth factor TKIs as therapy for advanced non-small cell lung cancer (NSCLC) have been reported to be infrequently associated with heart failure and QT prolongation.

Summary While tyrosine kinase inhibitors have been demonstrated to increase overall survival across different types of cancers, special consideration should be given to cardiovascular toxicities. High-risk patients can be identified by undergoing a comprehensive workup at baseline.

Keywords Tyrosine kinase inhibitor · Cardiovascular toxicity · Vascular endothelial growth factor · BCR-ABL · Bruton tyrosine kinase

Introduction

Over the last decade, the approval of tyrosine kinase inhibitors (TKI) has completely shifted the treatment paradigm for several cancer types. Under normal circumstances, tyrosine kinases play an essential role in cellular growth, differentiation, and metabolism [1]. However, tyrosine kinases become dysregulated or constitutively activated in tumor cells due to several factors such as point mutations, gene fusions, and the abundance of ligands. Tyrosine kinase inhibition has been shown to be an essential step in managing most

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hematologic malignancies and some solid tumors. Nevertheless, the off-target actions of tyrosine kinase inhibitors produce significant toxicities [1]. In this review, we aim to describe the adverse cardiovascular profiles of four major classes of TKIs, i.e., Bruton TKIs, breakpoint cluster region (BCR)-ABL-gene TKIs, vascular endothelial growth factor receptor (VEGF-R) TKIs, and epithelial growth factor receptor (EGF-R) TKIs. It is impossible to cover every existing TKI; readers are directed to the US FDA label for agent-specific treatment guidelines.

Bruton's Tyrosine Kinase Inhibitors

BTK is normally involved in B cells' maturation and immunoglobulin synthesis through the B cell receptor (BCR) pathway. However, it plays a significant role in their malignant proliferation, survival, adhesion, and migration. Inhibition of BTK has been shown to improve the survival of patients with B cell malignancies. Ibrutinib was the first BTK inhibitor to receive FDA approval for the treatment of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), Waldenström macroglobulinemia, mantle cell lymphoma, chronic graft vs. host disease, and 17 p deletion CLL [2–7]. Acalabrutinib, a second-generation BTK inhibitor, has been shown to be more selective than ibrutinib, resulting in a better side effect profile. It received FDA approval for treating relapsed or refractory mantle cell lymphoma, as well as breakthrough therapy designation for adults with CLL or SLL [8].

Atrial Fibrillation

The underlying mechanism of BTK inhibitor-mediated atrial fibrillation (AF) has been linked to concomitant inhibition of PI3K-Akt signaling, involved in normal cardiac response to stressors [9]. The low rates of AF observed with acalabrutinib compared to the less selective ibrutinib suggest the implication of other signaling pathways [10]. In experimental models, Jiang and colleagues reported an association with increased left atrial fibrosis, Ca^{2+} handling modifications, enhanced delayed after depolarization, and increased CaMKII expression [11]. In a recent study by Xiao and colleagues, AF was induced in mice receiving ibrutinib but not in those receiving acalabrutinib. The inhibition of the C-terminal Src kinase (CSK) with atrial remodeling was demonstrated to be a possible mechanism [12•].

The rate of AF of any grade has ranged from 5 to 16% in trials investigating ibrutinib [13]. RESONATE and RESONATE-2 were the first phase 3 trials to report this adverse event. RESONATE compared ibrutinib to ofatumumab in patients with relapsed or refractory CLL or SLL. At a 19-month follow-up, 7% of patients on the ibrutinib arm experienced AF, among which 3.6% were grade ≥ 3 [14]. RESONATE-2 evaluated the efficacy of first-line ibrutinib versus chlorambucil in patients aged ≥ 65 years with either CLL or SLL. In the 5-year follow-up analysis, 16% of patients in the ibrutinib arm experienced AF, of which 5% were grade ≥ 3 [15]. Similarly, a single-center retrospective study of 582 patients treated with ibrutinib showed an incidence of AF of 16% after a median follow-up of 32 months [16]. Yet, in a prospective ECG-based study, nearly 38% developed AF [17]. Cancer focused trials involving acalabrutinib reported lower frequencies (less than 10%) [8, 18]. Most cases are diagnosed within 8 months of exposure to a BTK inhibitor [13].

Several risk factors for ibrutinib-mediated AF have been identified. The strongest association was a previous history of AF and age > 65 years. Looser correlations were described with the following factors: hypertension, hyperlipidemia, and pre-treatment evidence of left atrial enlargement (either on EKG or a left atrial volume index of ≥ 40 mL/m^2 on transthoracic echocardiogram) [19–21]. In patients without a history of AF, older age, hypertension, and previous treatment with certain antihypertensives (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers) and aspirin appear to be associated with the occurrence of ibrutinib-mediated AF [22].

While the CHA2DS2-VASc score is used to predict the stroke risk in patients with new-onset AF while on a BTK inhibitor, the validity of this score in cancer patients is not well established [23]. In a patient with a score ≥ 2, treatment suspension should be considered until AF is controlled. Rate control with a beta-blocker is usually preferred over a non-dihydropyridine calcium channel blocker or rhythm control with amiodarone due to the interaction with cytochrome P4503A4 and possible reduction in ibrutinib metabolism. The initiation of anticoagulation depends on the evaluation of both stroke and bleeding risk (ibrutinib is associated with an increased risk of bleeding through its antiplatelet effect). A common strategy would be to start anticoagulation in patients with a CHA2DS2-VASc > HAS-BLED score. Preferred regimens include low-dose apixaban (2.5 mg twice daily) or regular enoxaparin [24]. Vitamin K antagonists are usually avoided due to the risk of fatal subdural hematoma [25].

Ventricular Arrhythmias

The occurrence of ventricular arrhythmias and sudden cardiac death in patients treated with ibrutinib is uncommon, but a high suspicion index should be maintained. Symptoms of dizziness, palpitations, and syncope should be promptly investigated and may warrant inpatient admission to a telemetry unit. In a large retrospective, multicenter study including 582 patients with hematologic

malignancies treated with ibrutinib, the incidence of ventricular arrhythmia has been estimated at around 596 per 100 000 person-years with a median time to event of 16 months [26]. This effect is likely not associated with a prolongation of the corrected QT (QTc) interval, as ibrutinib is known to produce QT shortening [27]. Additional patient-level data is needed to assess ventricular arrhythmic risk with next-generation BTK inhibitors.

Hypertension

The development of hypertension is a common side effect of BTK inhibitors, particularly ibrutinib. In a pooled safety analysis of four randomized controlled trials involving 756 patients with SLL/CLL or mantle cell lymphoma treated with ibrutinib, the incidence of new-onset grade ≥ 3 hypertension was 4% with a median time to event of 4.6 months [28]. A single-center retrospective study including 562 patients with B cell malignancies treated with ibrutinib reported an incidence of new-onset or worsening hypertension of 78.3% over a median follow-up of 30 months. On multivariate analysis, new-onset or worsening hypertension was associated with a higher occurrence of other major adverse cardiovascular events (MACEs, particularly AF). The initiation of antihypertensive therapy has been shown to decrease this risk [29]. Further, elevation in the risks for incidence hypertension was recently seen in a retrospective evaluation of 280 acalabrutinib-treated patients, with nearly 54% developing new hypertension [30]. This suggests hypertension may be a class effect of these agents. Additionally, hypertension at baseline should be optimally managed. The suggested underlying mechanism is a reduction in nitric oxide production by inhibiting PI3K/Akt signaling [9].

In a population-based study including 1556 patients with CLL, the 3-year cumulative risk of heart failure was 7.7% with ibrutinib versus 3.6% in controls [31•].

BCR-ABL Tyrosine Kinase Inhibitors

BCR-ABL is a chimeric protein with constitutive tyrosine kinase activity resulting from a gene fusion that drives chronic myeloid leukemia (CML). The inhibition of BCR-ABL tyrosine kinase using small molecule TKIs resulted in improved survival matching sometimes the general population. However, associated adverse cardiovascular events are commonly reported.

Imatinib

Imatinib is a first-generation BCR-ABL TKI that additionally targets platelet-derived growth factor receptors (PDGFR) and the c-KIT gene. It has been demonstrated to have the best adverse events profile among the BCR-ABL TKIs from a cardiovascular perspective, with data actually suggesting a cardioprotective effect. In a retrospective cohort study including 2390 patients with CML, the use of imatinib has been associated with a significantly lower rate of peripheral arterial occlusive disease (PAOD) compared with placebo or nilotinib [32]. In a randomized trial involving patients with pulmonary hypertension (PAH) who remain symptomatic on a two-drug regimen, the use of imatinib as an add-on therapy resulted in a significantly improved right ventricular function on echocardiography [33]. In preclinical models, imatinib was associated with lower blood glucose levels, fewer atherosclerotic lesions, and less in-stent restenosis [34]. Some studies suggest an increased incidence of heart failure with the long-term use of imatinib; however, the data remain inconclusive [35, 36]. The National Comprehensive Cancer Network (NCCN) guidelines only recommend assessment of baseline left ventricular function in patients with underlying cardiac disease or risk factors for heart failure who are starting therapy with imatinib [37].

Second-Generation Agents

Dasatinib has been associated with type I pulmonary hypertension (PAH). The most likely mechanisms are an attenuation of the vasoconstrictive response to hypoxia and endothelial remodeling. Notably, higher levels of circulating endothelial adhesion molecules (sICAM-1, sVCAM-1, and sE-selectin) have been reported in patients with CML treated with dasatinib [38]. The French Pulmonary Hypertension Registry reported an incidence of 0.45% among patients with chronic dasatinib exposure, with a relative improvement of symptoms after discontinuation [39]. While most studies show that dasatinib-induced PAH is reversible, others report worsening symptoms as well as permanent vascular damage after cessation of therapy [40, 41]. Dasatinib has also been associated with fluid retention (peripheral edema and pleural effusion), not to be confused with symptoms of congestive heart failure [42].

Nilotinib is a more selective BCR-ABL1 TKI than imatinib resulting in a deeper and faster treatment response in patients with CML. Nilotinib may induce a prothrombotic state linked to the occurrence of ischemic events. In the 10-year update of the ENESTnd trial, cardiovascular events, including ischemic heart disease, cerebrovascular events, and peripheral arterial disease, have been more frequently reported in the nilotinib arms than in the imatinib arm (16.5 and 23.4% versus 3.6%) [43••]. These effects might be related to higher serum levels of proinflammatory cytokines (TNF-α and IL-6) as well as cellular adhesion molecules [44]. Hyperglycemia and dyslipidemia have also been associated with nilotinib [39]. Suggested pathogenic

mechanisms include the downregulation of adipogenic genes (*Ppar-γ*, *Lpin1*, and *Srebp1*) as well as a reduction in adipokine expression [45].

Bosutinib is a second-generation BCR-ABL1 TKI with a safety profile similar to imatinib. In a retrospective study including 570 patients with imatinib-refractory CML treated with bosutinib, the rate of any cardiac event was 18%. The collective rate of heart failure, ischemic heart disease, and PAOD was less than 4% [46].

Third-Generation Agents

Ponatinib is perhaps the most potent BCR-ABL TKI. It inhibits the kinase activity of Bcr-Abl even in the presence of the highly resistant T315I mutation, but it also has off-target effects, notably inhibiting VEGF-R. Its use has been strongly associated with several ischemic adverse events. In the first analysis of the PACE trial, among the 267 patients with chronic phase CML treated with ponatinib, the incidence of cardiovascular, cerebrovascular, and peripheral arterial occlusive events was 7.1, 3.6, and 4.9%, respectively [47]. In the 5-year follow-up report of this trial, the cumulative incidence of treatment-related arterial obstructive events was as high as 31%. The presence of hypertension, diabetes, hypercholesterolemia, obesity, and a history of any cardiac disease were identified as risk factors [48]. In the OPTIC study investigating different doses of ponatinib (15, 30, and 45 mg), the occurrence of cardiac toxicity was not dose-dependent [49]. Both the PACE and OPTIC studies mentioned high rates of heart failure (12 and 9%, respectively) and arrhythmia (15 and 7%, respectively; mainly AF but also ventricular arrhythmias, bradycardia, QTc prolongation, atrioventricular blocks, and cardiac arrest) [48, 49]. For these reasons, patients should undergo a careful benefit-risk evaluation before initiating ponatinib and close monitoring of symptoms if treatment is started. Asciminib is effective in Ph + CML that failed other BCR-ABL TKIs or that harbors a T315I mutation. Its use has been linked to arterial ischemic events (13%), cardiac failure (2.2%), hypertension (19%), and QTc prolongation (7%) [50]. In a phase III trial involving patients with CML refractory to at least two TKIs, asciminib showed higher rates of hypertension and peripheral edema than bosutinib (11.5 versus 3.9% and 5.8 versus 2.8%, respectively) [51].

Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors

Vascular endothelial growth factor receptor (VEGFR) TKIs are orally active small molecule blocking angiogenesis. Their use has been approved in different settings such as renal cell carcinoma (RCC), thyroid cancer, soft tissue sarcoma, colorectal cancer, hepatocellular carcinoma, melanoma, gastrointestinal stromal tumor (GIST), and non-small cell lung cancer (NSCLC) [52]. From a cardiovascular toxicity perspective, VEGFR TKIs are most strongly linked to hypertension and thromboembolic events [53].

VEGF-R TKI-related hypertension is mainly due to a decrease in nitric oxide production, as VEGF plays an important role in its synthesis. Some preclinical studies show an associated increase in endothelin-1 concentrations. Remarkably, the renin–angiotensin–aldosterone (RAA) system does not seem to play a significant role. Another purported mechanism is the rise in systemic resistance due to a reduction in neo-angiogenesis [54]. A multicancer retrospective study identified older age (≥ 60 years), pre-existing hypertension, and a body mass index ≥ 25 kg/m^2 as independent risk factors [55]. In a meta-analysis of 13 clinical trials investigating sunitinib, the rate of all-grade and high-grade hypertension among the 4999 participants was 21.6% and 6.8%, respectively, with a relative risk (RR) of 22.72 (95% CI: 4.48 to 115.29, $p < 0.001$) for high-grade hypertension [56]. In 2016, another large-scale meta-analysis of 72 randomized trials (30,013 participants) showed similar rates of all-grade (23%) and high-grade hypertension (4.4%) with VEGF-R-TKIs [57]. In the AXIS trial, the rate of all-grade hypertension was higher in the axitinib arm than in the sorafenib arm in patients with metastatic RCC (40 vs. 29%, respectively) [58]. Of all VEGF-R-TKIs, pazopanib is associated with the highest rates of high-grade hypertension (36%) [59]. Management of hypertension associated with VEGF-R inhibitors includes optimization of pre- and post-treatment blood pressure (< 130/80 mmHg), favoring ACE inhibitors over calcium channel blockers (due to drug interaction), and regular blood pressure monitoring [52].

The pathophysiology of thromboembolism in patients taking VEGFR-TKIs most likely involves a reduction in nitric oxide production, normally responsible for the reduction in platelet and leukocyte adhesion as well as the inhibition of smooth muscle cell proliferation [60, 61]. In a large meta-analysis of 10 clinical trials, including 10,255 patients with advanced cancers treated with sorafenib or sunitinib, the incidence of arterial thromboembolic events (peripheral, cerebral, and cardiovascular) was reported to be 1.4%, with a RR of 3.03 (95% CI, 1.25 to 7.37; $p = .015$) compared to controls, independent of tumor type [62]. Data concerning the association with venous thromboembolism are controversial [63]. Controlling cardiovascular risk factors such as hypertension, diabetes, and hypercholesterolemia is recommended before and after the initiation of treatment. Prophylaxis with low-dose aspirin should be considered in high-risk patients (Table 1) [64].

New-onset heart failure has been linked to the use of VRGF-R-TKIs. In a 2018 multicancer meta-analysis of 29,252 patients from 71 trials, RR after VEGF-R-TKI

Table 1 Baseline cardiovascular risk assessment of high and very high-risk patients treated with vascular endothelial growth factor inhibitors[a] or BCR-ABL tyrosine kinase inhibitors[b] as per the European Society of Cardiology and the International Cardio-Oncology Society 2020 position statement

Vascular endothelial growth factor inhibitors[a]	
Risk factor	**Magnitude**
• Heart failure or cardiomyopathy	Very high risk
• Arterial vascular disease (ischemic heart disease, percutaneous coronary intervention, coronary artery bypass graft, stable angina, transient ischemic attack, stroke, peripheral vascular disease)	Very high risk
• Venous thrombosis (deep venous thrombosis or pulmonary embolism)	High risk
• Baseline left ventricular ejection fraction < 50%	High risk
• QTc ≥ 480 ms	High risk
• Age ≥ 75 years	High risk
• Systolic blood pressure > 140 mmg Hg or diastolic blood pressure > 90 mm Hg or on treatment	High risk
• Prior anthracycline exposure	High risk
Second- and third-generations BCR-ABL tyrosine kinase inhibitors (TKI)[b]	
Risk factor	**Magnitude**
• Arterial vascular disease (ischemic heart disease, percutaneous coronary intervention, coronary artery bypass graft, stable angina, transient ischemic attack, stroke, peripheral vascular disease)	Very high risk
• Arterial thrombosis with previous TKI	Very high risk
• Heart failure or left ventricular systolic dysfunction	High risk
• BCR-ABL TKI-mediated LVSD	High risk
• Ankle-brachial pressure index ≤ 0.9	High risk
• Pulmonary arterial hypertension: peak systolic PA pressure at rest ≥ 35 mmHg on echography	High risk
• Baseline left ventricular ejection fraction < 50%	High risk
• QTc ≥ 480 ms	High risk
• Cardiovascular disease 10-year risk score > 20%	High risk
• Age ≥ 75 years	High risk
• Current smoker or significant smoking history	High risk

[a] and [b] are adapted from Lyon AR, et al. Eur J Heart Fail 2020; 22(11):1945–1960, with permission from John Wiley and Sons [99]

therapy was 2.53 (95% CI: 1.79–3.57; $p < 0.001$), with the highest incidence reported with sunitinib and patients with hepatocellular carcinoma [65]. Another analysis showed that high-grade congestive heart failure occurred in 1.4% of cases with an odds ratio (OR) of 3.51 (95% CI 1.74–7.05, $p < 0.001$) compared to placebo [66]. Baseline and post-treatment, left ventricular function should be assessed in high-risk patients (presence of cardiovascular risk factors, underlying cardiac disorder, prior exposure to cardiotoxic agents, older age), and discontinuation of VEGF-R-TKI should be considered in the evidence of echocardiographic or clinical cardiac dysfunction.

Vandetanib and lenvatinib have the strongest association with the occurrence of QTc prolongation, predisposing to torsades de pointe and eventually ventricular arrhythmias [67, 68]. The Framingham formula can be used to calculate QTc in this setting [69]. Special consideration should be given to patients with underlying electrolyte abnormalities and those concomitantly receiving other QT-prolonging agents (mainly antiarrhythmics).

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase in the erythroblastic leukemia viral oncogene homolog (ErbB)/HER (human epidermal growth factor receptor) family of transmembrane glycoprotein receptors [70]. EGFR-TKIs are small molecules that have been proven to be beneficial, targeted therapies for NSCLC due to the expression of EGFR in 50–90% of NSCLC cases [71].

First-Generation EGFR-TKIs

Gefitinib and erlotinib are first-generation oral, selective EGFR-TKIs that compete with ATP for binding to the tyrosine kinase domain [72]. While gefitinib and erlotinib were originally reported to have no association with cardiovascular adverse effects [73, 74], a few have been described in the more recent literature.

Table 2 Management of cardiovascular toxicities per agent

Agent	Toxicity	Management
Bruton tyrosine kinase inhibitors	Atrial fibrillation	Discontinuation until controlled Rate control with a beta-blocker Anticoagulation (apixaban or enoxaparin) if CHA2DS2-VASc > HAS BLED
	Ventricular arrhythmia	Discontinuation Continuous cardiac monitoring
	Hypertension	Optimization of baseline blood pressure Initiation of hypertensive therapy
BCR-ABL inhibitors		
Dasatinib	Pulmonary hypertension	Echocardiography every 3 months Discontinuation
Nilotinib, ponatinib	Arterial ischemic events	Risk factors control with statins, antihypertensives, and antidiabetics Ankle-brachial index or duplex ultrasound monitoring every 6–12 months Discontinuation
Vascular endothelial growth factor receptor tyrosine kinase inhibitors	Hypertension	Optimization of baseline blood pressure Initiation of hypertensive therapy: preferably ACE inhibitors
	Thromboembolism	Risk factors control with statins, antihypertensives, and antidiabetics Prophylaxis with low-dose aspirin should be considered in high-risk patients Discontinuation
	Heart failure	Baseline left ventricular ejection fraction Close monitoring for symptoms Discontinuation
	QTc prolongation	Holding other QTc prolonging drugs Discontinuation
EGFR inhibitors		
Gefitinib	Myocardial infarction	Per STEMI/NSTEMI guidelines – DAPT ± GPIIbIIIa inhibitors, anticoagulation, statin therapy Discontinuation
	Cardiomyopathy (cancer therapeutics-related cardiac dysfunction (CTRCD))	GDMT (beta blocker, ACEi/ARB/ARNI) Discontinuation Obtain baseline left ventricular function
Erlotinib	Myocardial ischemia/infarction	Per STEMI/NSTEMI guidelines Discontinuation
	Venous thromboembolism	Anticoagulation
Afatinib	Cardiomyopathy	GDMT Discontinuation
	Hypotension	Monitor for symptomatic hypotension Discontinuation
Osimertinib	Acute coronary syndrome	Per STEMI/NSTEMI guidelines Discontinuation
	CTRCD	Obtain baseline left ventricular assessment GDMT Discontinuation; consider dose reduction in patients with EGFR mutation
	QTc prolongation	Avoid QTc prolonging medications Correct electrolyte abnormalities, treat bradycardia Avoid if family history of sudden cardiac death or congenital long QT syndrome Discontinuation if QTc > 500 ms

Gefitinib

Acute and recurrent myocardial infarction from platelet activation-induced thrombosis in patients on gefitinib therapy has been reported [75, 76]. Gefitinib-induced cardiomyopathy [77] and myocarditis [78] have also been described. In murine models, gefitinib has been shown to induce cardiotoxicity through the upregulation of hypertrophic gene markers such as brain natriuretic peptide (BNP) and beta-myosin heavy chain (β-MHC), and the downregulation of the antihypertrophic gene α-MHC, resulting in cardiac hypertrophy and ultimately apoptotic cardiomyocyte cell death due to increased expression of apoptotic mediators caspase-3 and p53 [79]. In a nested case–control analysis of a cohort of 27,992 patients, gefitinib and erlotinib were not associated with significant odds of developing heart failure [80].

Erlotinib

A higher incidence of myocardial ischemia and myocardial infarction was demonstrated in patients on combination erlotinib/gemcitabine therapy (2.3%) compared to gemcitabine monotherapy (1.2%) in a phase III trial of 569 patients comparing therapies for locally advanced or metastatic pancreatic adenocarcinoma [81]. Pancreatic cancer is a highly thrombogenic malignancy with a reported 25% venous thromboembolic (VTE) incidence which peaks during chemotherapy [82]. In the same phase III trial, a greater rate of venous thromboembolic events was reported in the erlotinib/gemcitabine combination group (3.9%) compared to the gemcitabine monotherapy group (1.2%). Based on these findings, erlotinib is proposed to be associated with acute coronary events and venous thromboembolism [83].

Dilated cardiomyopathy (DCM) has been described with erlotinib use as maintenance therapy after initial treatment with cisplatin/pemetrexed for metastatic NSCLC [84]. Despite the discontinuation of erlotinib therapy and initiation of guideline-directed medical therapy (GDMT), a return to baseline cardiac function was not observed. Erlotinib is however no longer used for maintenance therapy. When chosen over preferred maintenance therapy, pemetrexed, due to poor Eastern Cooperative Oncology Group Performance Status (ECOG PS), this may be confounding, as poor PS may be independently associated with DCM.

Myocardial infarction, arterial thromboembolic events, cardiopulmonary arrest, and cardiopulmonary failure have also been rarely associated with erlotinib therapy [85–87].

Second-Generation EGFR TKIs

Afatinib

Afatinib is a highly selective, potent, and irreversible protein kinase inhibitor of both EGFR and HER2 kinases [83]. Given

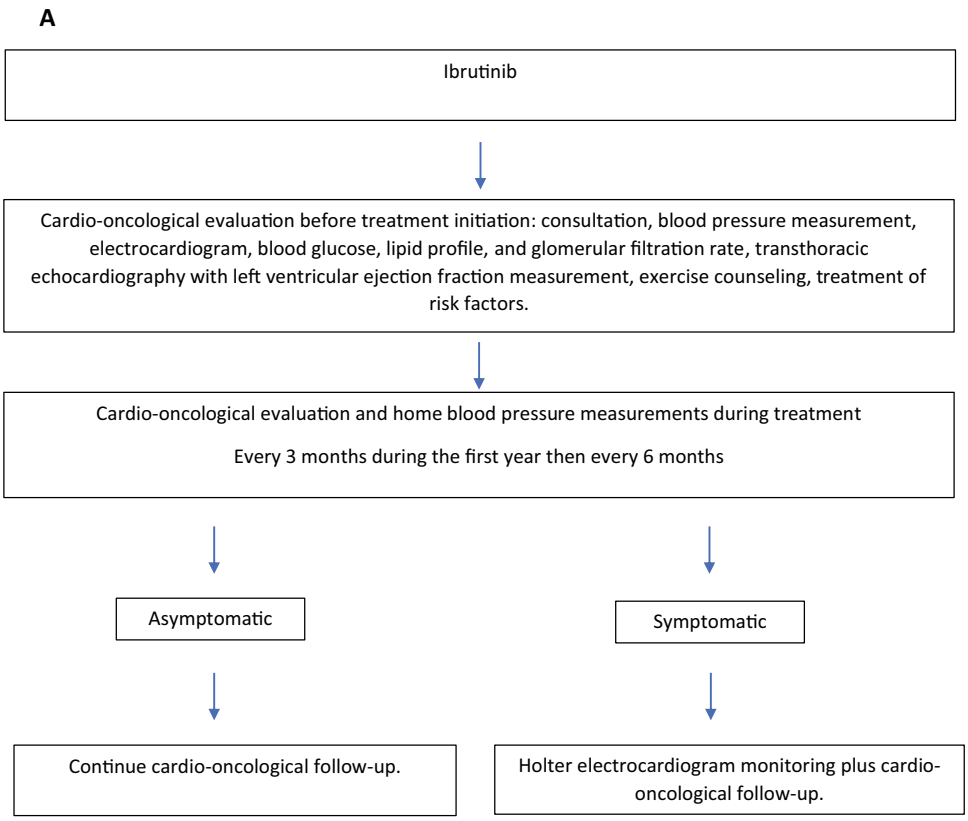
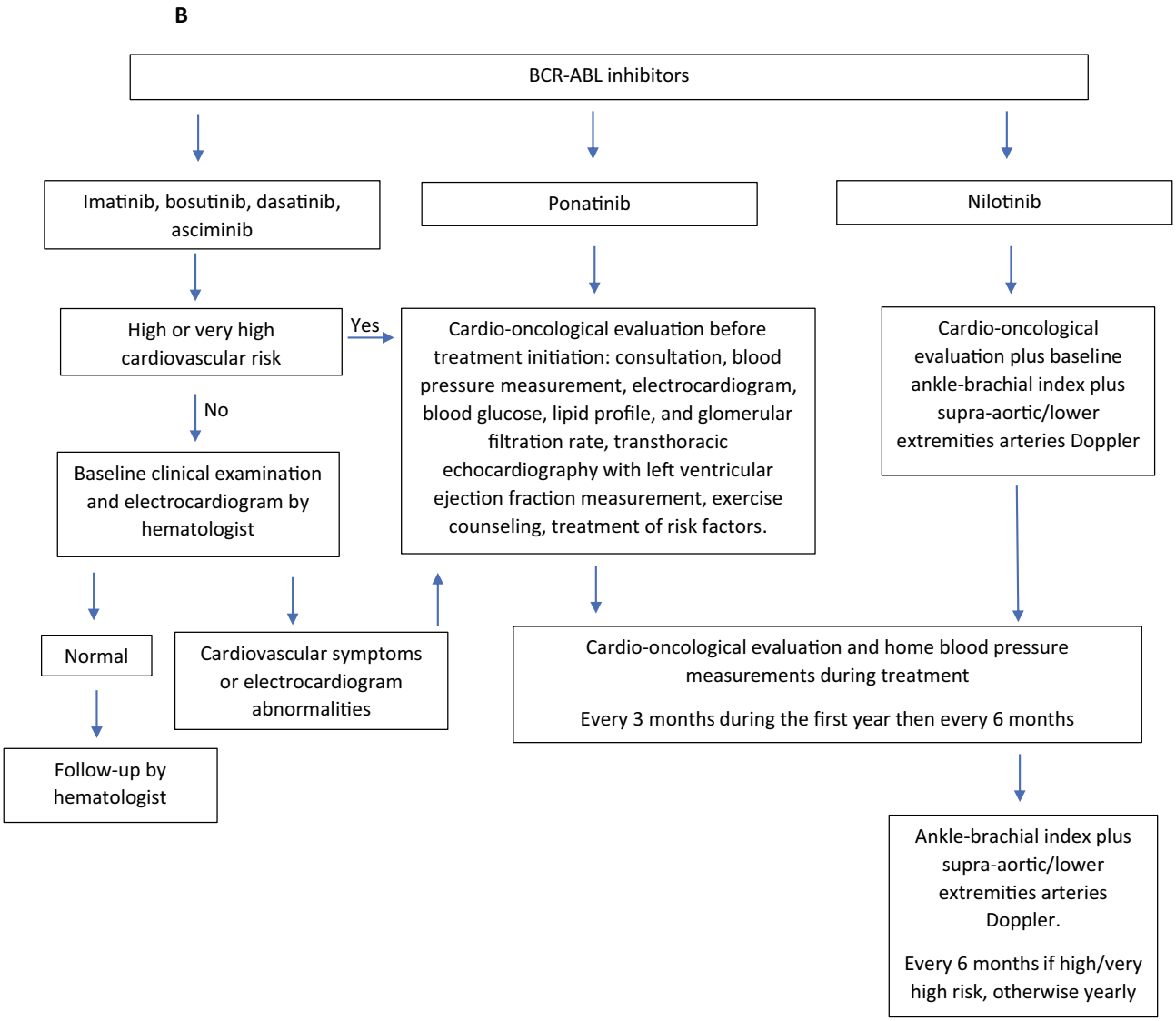


Fig. 1 Monitoring approach concealing both European and American guidelines suggested by the French Working Group of Cardio-Oncology in patients receiving ibrutinib (**A**), BCR-ABL inhibitors (**B**), and vascular endothelial growth factor receptor tyrosine kinase inhibitors (**C**) (adapted from: Alexandre J, et al. *J Am Heart Assoc* 2020;9(18):e018403, with permission from the authors) [100]

Fig. 1 (continued)



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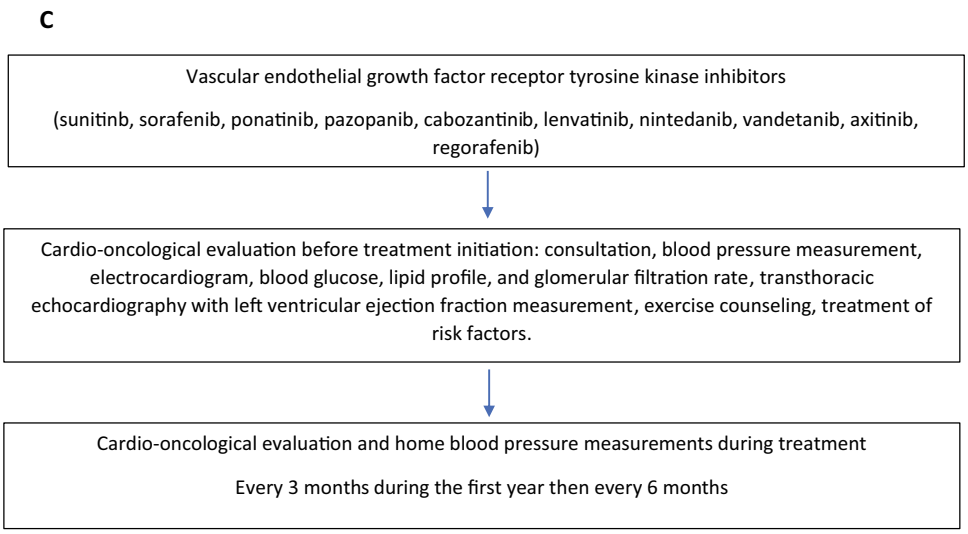

the known cardiac dysfunction associated with HER 2 inhibition, there were initial concerns regarding the cardiac safety profile of afatinib. However, an analysis of trials providing a cohort of 3865 afatinib-treated patients showed comparable cardiac side effects with placebo. The frequency of cardiac failure (acute left ventricular failure, left ventricular failure, high output cardiac failure) ranged between 1.0 and 2.2%, with common terminology criteria for adverse events (CTCAE) grade>/=3 ranging between 0 and 1.0% (stage C or D, heart failure, or death) [88]. Afatinib-associated cardiomyopathy and afatinib-induced hypotension have subsequently been reported, both of which resolved upon interruption of afatinib therapy [89, 90].

Third-Generation EGFR-TKIs

Osimertinib

Osimertinib is an oral, selective, irreversible third-generation EGFR-TKI developed for patients with EGFR-sensitizing mutations and resistance to EGFR T790M mutations [91].

Of the EGFR-TKIs, it has the most significant cardiovascular risk profile.

In a retrospective single-center study of 123 patients with advanced EGFR-mutant NSCLC, osimertinib treatment was associated with a 4.9% incidence of grade 3 or higher CTCAE, including acute myocardial infarction (1), heart failure with reduced ejection fraction (3), and valvular heart disease (2) (severe mitral regurgitation, severe tricuspid regurgitation). Notably, all but one of the patients with adverse cardiac events had preexisting cardiovascular disease conditions [92].

Discontinuation of osimertinib therapy in patients who developed cancer therapeutics-related cardiac dysfunction (CTRCD), and treatment with guideline-directed medical therapy, resulted in the return of LVEF to baseline in all patients, except those with severely reduced LVEF.

In a meta-analysis of two randomized controlled trials with a cohort of 971 patients, osimertinib-treated patients were 2.7 times more likely to develop cardiac failure [93].

Histopathological examinations from patients with CTRCD revealed cardiomyocyte hypertrophy and lipofuscin deposits, suggesting that osimertinib may produce functional inhibition of myocyte contractility without significant cell death or inflammation [92].

While the FLAURA trial reported grade 3 or higher QTc interval prolongation in 1% of patients [94], a post-marketing surveillance study in over 3500 Japanese patients showed a 0.1% incidence [95]. A meta-analysis by Thein et al. demonstrated that osimertinib-treated patients were 2.6 times more likely to develop QT prolongation. In a real-world Japanese population, the average QTc was significantly prolonged from 421.9 + / − 23.0 ms to 442.4 + / − 33.2 ms over a median of 116 days. No fatal arrhythmias have been reported [93]. Atrial fibrillation (4%) and pericardial effusion (8.2%) [96, 97] have also been reported with osimertinib use.

Preexisting heart disease is a predictor of osimertinib-associated cardiotoxicity [92, 98]. Obtaining a thorough past medical history, assessment of cardiac function with an echocardiogram and QTc assessment with an electrocardiogram is recommended prior to and after initiation of osimertinib therapy. CTRCD from osimertinib is reversible with drug withdrawal. Therefore, discontinuing therapy upon detection of cardiac dysfunction, and GDMT initiation, is advised. Permanent discontinuation, especially in cases with a severe LVEF reduction, and temporary interruption with reinitiation at the original or lower dose, should be considered based on patient preference and the presence of EGFR mutations.

Cardiovascular management strategies for each of the classes of drugs are summarized in Table 2 and Fig. 1.

Conclusion

In conclusion, despite the undeniable life-prolonging effects of TKIs, special consideration should be given to patients at high cardiovascular risk. A careful assessment of the benefit:risk ratio should be undertaken when considering these drugs. Co-morbidities and other risk factors that may increase the risk of these complications should be assessed and managed throughout the course of therapy, and concomitant administration of other drugs that may increase the risk of such events should be discouraged whenever possible.

Compliance with Ethical Standards

Conflict of Interest Neeraj Agarwal reports personal fees from Astellas, Astra Zeneca, Aveo, Bayer, Bristol Myers Squibb, Calithera, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Foundation Medicine, Genentech, Gilead, Janssen, Merck, MEI Pharma, Nektar, Novartis, Pfizer, Pharmacyclics, Seattle Genetic. They also report grants from Astellas, Astra Zeneca, Bavarian Nordic, Bayer, Bristol Myers Squibb, Calithera, Celldex, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Gilead, Glaxo Smith Kline, Immunomedics, Janssen, Medivation, Merck, Nektar, New Link Genetics, Novartis, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Seattle Genetics, Takeda, and Tracon, outside the submitted work. Daniel Addison reports grants from American Heart Association, NHLBI-NIH, and Pelotonia, outside the submitted work. Jorge Cortes reports grants and personal fees from BMS, Novartis, Pfizer, Takeda, Daiichi, Jazz Pharmaceuticals, Merus, and Forma Therapeutics; grants from Astellas and Amphivena; and personal fees from BiolineRx and Bioptah, outside the submitted work. Neal L Weintraub reports grants from NIH-NHLBI and the American Heart Association, outside the submitted work. Nazish Sayed reports grants from NIH-NHLBI and the American Heart Association, outside the submitted work. Avirup Guha reports personal fees from Pfizer/Myovant and grants from the American Heart Association, outside the submitted work. The other authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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