Cardio-Oncology Updates | *FAST FACTS*

KINASE INHIBITORS AND ASSOCIATED CARDIOTOXICITIES

KINASE INHIBITOR	ASSOCIATED CARDIOTOXICITIY[1]
Tyrosine Kinase Inhibitors (TKIs)	
Nilotinib	QT prolongation (<10%), hypertension (HTN; 10%-11%), ischemic heart disease (5%-9.4%), peripheral arterial occlusive disease (PAOD; 2.9%-3.6%), ischemic cerebrovascular events* and myocardial infarction (MI; <1%)
Dasatinib	Congestive heart failure (CHF) or left ventricular dysfunction (LVD; 2%-4%), QT prolongation (1%), pericardial effusion (3%-4%), palpitations (1%-10%), edema (generalized, 1%-4%; localized, superficial 3%-22%), pulmonary arterial HTN (PAH; 0.45%)
Pazopanib	HTN (40%-42%, grade 3-4 4%-7%; bradyarrhythmia (2%-18%), QT prolongation (0.2%-2%), CHF (1%), MI (2%)
Sunitinib	HTN (15%-39%), LVD (11%-27%); QT prolongation (<0.1%), peripheral edema (10%-24%)
Ponatinib	HTN (53%-71%), PAOD (12%), heart failure (6%-15%), cardiomyopathy and myocardial ischemia (21%), atrial fibrillation (AFib; 7%), bradyarrhythmia (1%), cardiac dysrhythmia (19%), peripheral edema (13%-22%)
Ibrutinib (Bruton TKI)	AFib/flutter (6%-15%), HTN (11%-20%), ventricular tachyarrhythmias (1%)
Acalabrutinib (Bruton TKI)	AFib (3%-5%)
Multikinase Inhibitors	
Cabozantinib	HTN (28%-36%)
Sorafenib	HTN (19.1%), CHF (1.9%), QT prolongation (<0.1%)
EGFR Inhibitors	
Lapatinib	LVD (grade 1 or 2, 1.52%-3.98%; grade 3 or 4, 0.51%-0.91%), QT prolongation/ torsades de pointes (<1%)
Vandetanib	HTN (33%), QT prolongation (14%), CHF (0.9%)

* Risk increases over time.[2,3]

Patient Risk Factors

Prior to initiating kinase inhibitor therapy, patients should be assessed for risk factors and underlying comorbidities to determine the most appropriate agent:

- Advanced age, race, history of cardiovascular disease, diabetes, kidney disease, hypertension, hyperlipidemia
- Prior lines of therapy with cardiotoxic effects
- Dose intensity
- Drug-drug or drug-food interactions

For certain kinase inhibitors, such as nilotinib and ponatinib, the risk increases over time for certain cardiac events.

Monitoring/Management Strategies

Kinase inhibitors have differing safety profiles with regard to cardiovascular, metabolic, and pulmonary toxicities. In addition to the monitoring/management strategies listed below, consider referring to cardio-oncology or cardiology.

QT prolongation	• More common in non–vascular endothelial growth factor signaling pathway (VSP) TKIs (e.g., nilotinib), but can also occur in VSP inhibitor TKIs (e.g., pazopanib, vandetanib) • Unique to nilotinib: – Patients should have electrocardiogram (ECG) monitoring at baseline, 7 days after therapy initiation, and as clinically indicated; drug-drug and drug-food monitoring; and ongoing monitoring/correction of serum potassium and magnesium concentrations during treatment. – Hold TKI if QTc prolongation is > 500 ms or a change from baseline of > 60 ms – Patients should avoid food 2 hours before and 1 hour after a kinase inhibitor dose, as food (especially high fat content) can prolong QT interval • Avoid concomitant treatment with QT-prolonging medications (e.g., antiarrhythmics [amiodarone, quinidine, procainamide], macrolide antibiotics [clarithromycin, azithromycin], fluoroquinolones [moxifloxacin, ciprofloxacin], antivirals [ganciclovir, foscarnet], antiemetics [ondansetron, dolasetron, domperidone])
Hypertension (HTN)	• Thorough screening for HTN before VSP inhibitor therapy initiation • Blood pressure at baseline and monitoring throughout therapy[4] • Patients with pre-existing HTN and multiple antihypertensive agents should be evaluated for renal dysfunction
AFib	• Unique to patients receiving ibrutinib or acalabrutinib; CHA_2DS_2-VASc score for clotting risk and HAS-BLED score for bleeding risk, as well as checking platelet count, may provide some guidance when considering anticoagulation • For chronic lymphocytic leukemia patients receiving warfarin, switch to another anticoagulant therapy.** • Echocardiogram to rule out structural heart disease • Thyroid profile to identify potential reversible cause of AFib
PAOD	• Ankle-brachial index measured at baseline and follow-up for PAOD with consideration for aspirin or clopidogrel • Manage risk factors for hypercholesterolemia: hypertension, diabetes, and smoking

PAH[5]	• Baseline chest x-ray and echocardiogram prior to initiating dasatinib, bosutinib, or lapatinib • Echocardiogram should be performed promptly in all patients who develop new or worsening dyspnea while receiving TKI treatment • Patients with severe symptoms (NYHA III–IV) should be considered for treatment with PAH-specific therapies such as PDE-5 inhibitors or parenteral prostanoids • Long-term surveillance is recommended with periodic echocardiography, even when PAH resolves
Arterial and occlusive events	No clear guidelines to prevent arterial thrombotic events in TKI therapy
Heart failure/ cardiomyopathy	• Obtain a baseline echocardiogram before initiating TKI • Monitor for symptoms of dyspnea or fluid overload, and repeat echocardiogram • Initiate clinical guideline-recommended heart failure medications (i.e., ACE inhibitors, beta blockers) if left ventricular ejection fraction < 50%
Cerebrovascular events	• Ponatinib and sunitinib are associated with vascular adverse events • Management of cerebrovascular events associated with TKIs should be tailored to specific situations, which are pathologically different from the more common causes of intracranial stenosis and thromboembolism • Exercise caution in patients with brain metastasis • Aggressive control of cardiovascular risk factors (hyperlipidemia), HTN, antiplatelet/anticoagulant agents • Consult with oncologist for a change or discontinuation of TKI • If secondary to intracranial stenotic disease, surgical treatment with a revascularization procedure may be an option
MI	• Aggressive management of cardiac risk factors prior to therapy (HTN, hyperlipidemia, diabetes) • Vigilant monitoring during nilotinib therapy • ECG at baseline, 7 days after initiation of treatment, and periodically following dose adjustments • Electrolyte levels should be monitored (hypokalemia and hypomagnesemia) throughout therapy • Dual antiplatelet therapy (aspirin [ASA], clopidogrel) should be used for patients with platelet counts >30,000/μL, and ASA only for platelet counts >10,000/μL. Below these values, an interdisciplinary evaluation is required to balance the risk of thrombosis with that of bleeding to decide on the therapeutic plan. • Percutaneous coronary intervention as appropriate

** Acalabrutinib may increase risk of hemorrhage in patients receiving anti-coagulant therapy; clinical trials did not include patients receiving warfarin.[6]

References

1. IBM Micromedex. https://www.micromedexsolutions.com/micromedex2/librarian/ssl/true. Accessed April 2020.
2. Hochhaus A, et al. *Leukemia*. 2016;30(5):1044-54.
3. Hughes TP, et al. ***Blood***. 2019;134(Supplement_1):2924.
4. James PA, et al. ***JAMA***. 2014;331(5):507-520.
5. Weatherald J, et al. ***Curr Opin Pulm Med***. 2017:23:392-397.
6. NCCN Clinical Practice Guidelines: Chronic Lymphocytic Leukemia Version 4.2020. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf