Overview and Management of Cardiac Adverse Events Associated With Tyrosine Kinase Inhibitors

DANIEL J. LENIHAN,^a PETER R. KOWEY^b

^aVanderbilt Heart and Vascular Institute, Nashville, Tennessee, USA; ^bJefferson Medical College and the Lankenau Institute for Medical Research, Main Line Health Heart Center, Wynnewood, Pennsylvania, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Cancer • Tyrosine kinase inhibitors • TKIs • Cardiac • Cardiovascular • Adverse events

Learning Objectives

Describe the cardiovascular adverse events associated with TKI therapy for cancer.

Develop strategies to minimize or mitigate CV adverse events during TKI treatment.

ABSTRACT

Background. Small-molecule tyrosine kinase inhibitors (TKIs) may provide an effective therapeutic option in patients with hematologic malignancies and solid tumors. However, cardiovascular (CV) events, including hypertension, heart failure, left ventricular systolic dysfunction, and QT prolongation, have emerged as potential adverse events (AEs) with TKI therapy.

Purpose. We review what is known about the mechanism of action of CV AEs associated with TKI use and discuss therapeutic interventions that may prevent and manage these events in clinical practice.

Methods. References for this review were identified through searches of PubMed and Medline databases, and only papers published in English were considered. Search terms included “cardiac,” “cardiovascular,” “cancer,” and “kinase inhibitor.” Related links in the databases were reviewed, along with relevant published guidelines.

Results. Although the link between rising blood pressure (BP) and CV AEs is observed but not proven, good clinical practice supports an aggressive policy on proper long-term BP management. There are insufficient data from randomized controlled clinical trials to show indisputably that aggressive or effective heart failure therapy in patients receiving TKIs will fundamentally change outcomes; however, clinical practice suggests that this is an effective long-term approach. Recognizing that QT prolongation is associated with TKI use facilitates identification of patients at high risk for this CV AE and increases awareness of the need for routine electrocardiograms and electrolyte monitoring for those receiving TKI treatment.

Conclusion. Regular monitoring, early recognition, and appropriate interventions for CV AEs can help more patients derive the benefit of long-term TKI therapy. *The Oncologist* 2013;18:900–908

Implications for Practice: Although the antitumor effects of small-molecule tyrosine kinase inhibitors (TKIs) can be considerable, these agents are often associated with cardiovascular (CV) adverse events (AEs), including hypertension, heart failure, and QT prolongation. This review covers the cardiac risks associated with different TKI therapies, including the putative mechanisms through which TKIs may affect cardiac function, as a means to increase both clinician awareness and understanding of these potential side effects in the oncology setting. This paper also provides clinical strategies for optimizing the use of TKI therapy based on careful pretreatment cardiac risk assessment, early recognition of CV AEs through regular monitoring of electrocardiograms and serum electrolytes, and aggressive management of cardiac events that develop in patients receiving TKI treatment. These guideline-based approaches can facilitate the appropriate use of TKI therapy, thereby allowing patients to experience long-term benefits while minimizing the occurrence of CV AEs.

INTRODUCTION

The use of small-molecule tyrosine kinase inhibitors (TKIs) in patients with hematologic malignancies and solid tumors may provide a therapeutic option that is effective and relatively easy to administer [1]. Some of these agents have improved patient outcomes and transformed the way many types of cancers are treated [2].

Cardiovascular (CV) events, including hypertension, heart failure, left ventricular (LV) systolic dysfunction, and QT prolongation, have emerged as potential adverse events (AEs) with small-molecule TKI therapy [3–8]. With a broad population of patients being treated with TKIs as well as increased patient survival and delayed tumor progres-

Correspondence: Daniel J. Lenihan, M.D., Vanderbilt Heart and Vascular Institute, 1215 21st Avenue South, Medical Center East, 5th Floor North Tower, Suite 5209, Nashville, Tennessee 37232-8802, USA. Telephone: 615-936-0335; Fax: 615-936-2158; E-Mail: daniel.lenihan@Vanderbilt.Edu Received December 12, 2012; accepted for publication June 17, 2013; first published online in *The Oncologist Express* on August 5, 2013. ©AlphaMed Press 1083-7159/2013/\$20.00/0 http://dx.doi.org/10.1634/theoncologist.2012-0466

Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE 4.03) grading severity of cardiac events associated with tyrosine kinase inhibitors [12]

Cardiac event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypertension	Prehypertension	Stage 1 hypertension—SBP 140–159 mmHg or DBP 90–99 mmHg; medical intervention indicated; recurrent or persistent (≥ 24 hours); symptomatic increase by >20 mmHg (DBP) or to $>140/90$ mmHg if previously within normal limits; monotherapy indicated	Stage 2 hypertension—SBP ≥ 160 mmHg or DBP ≥ 100 mmHg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death
Heart failure	Asymptomatic with laboratory (e.g., brain natriuretic peptide) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Left ventricular systolic dysfunction	—	—	Symptomatic due to drop in ejection fraction; responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, IV vasopressor support, or heart transplant indicated	Death
QT prolongation	QTc 450–480 ms	QTc 481–500 ms	QTc ≥ 501 ms on at least two separate electrocardiograms	QTc ≥ 501 ms or >60 -ms change from baseline and torsades de pointes, or polymorphic ventricular tachycardia, or signs or symptoms of serious arrhythmia	—

QT is the duration of ventricular depolarization and repolarization.

Abbreviations: —, no data; DBP, diastolic blood pressure; IV, intravenous; QTc, corrected QT interval; SBP, systolic blood pressure.

sion from improvements in cancer therapy, prevention and management of TKI-associated CV AEs will become increasingly important [6]. It is critical to recognize and appropriately manage these AEs to optimize TKI therapy and improve patient outcomes. This review focuses on CV AEs associated with the use of small-molecule TKIs and discusses therapeutic interventions to prevent and manage these events in clinical practice.

Overview of Cardiac Events

The Common Terminology Criteria for Adverse Events (CTCAE), developed by the National Cancer Institute (NCI), provides a system for the consistent description and grading of CV AEs observed during clinical trials of therapeutic agents [9]. The severity of CV AEs associated with TKIs was initially graded using the NCI CTCAE version 3.0 [10, 11]. One issue observed with using CTCAE version 3.0 outside clinical trials is that some of the included rating scales (e.g., hypertension grades) do not necessarily reflect the more typical classification systems used in clinical practice, and thus the usefulness of those rating scales for guiding patient-management decisions is limited [10].

Starting with CTCAE version 4.0 (released in May 2009) and continuing with the current version, CTCAE 4.03 (released in June 2010), the criteria for CV AEs have been revised and are shown in Table 1 [9, 12]. Hypertension is now graded according to the seventh and most recent guidelines from the Joint National Committee on Prevention, Detection, Evaluation,

and Treatment of High Blood Pressure (JNC 7) [9, 13]; the JNC 8 report is expected to be released in 2013 [14]. Heart failure became a new entry in CTCAE version 4.0, and the definition of LV systolic dysfunction was redefined solely on the basis of symptoms and interventions as well as limited to grades 3–5 [9]. Asymptomatic LV systolic dysfunction, defined previously on the basis of LV ejection fraction measurements, is now defined in terms of symptoms and appropriate interventions [9]. New criteria for QT prolongation have been adapted to align more closely with clinically relevant statistical definitions [9, 12, 15]. Table 2 [16–25] summarizes the frequencies of common CV AEs associated with TKI therapy (e.g., hypertension and reduction in LV ejection fraction) and provides information on the impact of these agents on the QT interval.

Hypertension

High blood pressure (BP) is associated with increased risk of cardiovascular complications, including stroke, myocardial infarction, and heart failure [10]. It has been established that TKIs, especially those that interfere with the vascular endothelial growth factor (VEGF) signaling pathways (VSPs; VSP inhibitors), have a class effect of raising BP significantly, and that effect correlates with CV AEs. Hypertension is an important consideration when treating patients with small-molecule TKIs (e.g., sunitinib, sorafenib, pazopanib, vandetanib, and cabozantinib) and monoclonal antibodies (e.g., bevacizumab) that inhibit the VEGF signaling pathway [9, 16, 26]. Interaction between the soluble VEGF and its primary receptor, VEGF receptor 2 (VEGFR-2), on endothelial cells leads to multiple important physiologic changes, including increased capillary permeability; upregulated nitric oxide production with secondary relaxation of vascular smooth muscle; and increased proliferation, migration, and survival of endothelial cells under stress [27]. Disruption of the VSP and subsequent angiogenesis can be affected by inhibition of the interaction between VEGF and VEGFR-2 on endothelial cells.

Experimental evidence suggests that VSP inhibitors, including TKIs, typically raise BP by increasing both vascular tone secondary to reduced nitric oxide production and increasing

Experimental evidence suggests that VSP inhibitors, including TKIs, typically raise BP by increasing both vascular tone secondary to reduced nitric oxide production and increasing vascular resistance secondary to endothelial cell damage and dysfunction. These effects of VSP inhibitors may be mediated by inhibiting the target receptor in another tissue or by inhibiting additional kinases in a different tissue.

Table 2. Cardiac-related adverse events associated with tyrosine kinase inhibitor therapy [16–25]

Frequency of hypertension and LV dysfunction					
	Hypertension				Reduction in LVEF
	Overall AEs with treatment	Grade 3/4 AEs with treatment	Overall AEs with placebo	Grade 3/4 AEs with placebo	
Small-molecule TKIs	(%)	(%)	(%)	(%)	
Cabozantinib [22]	33	8	4	9	NR
Lapatinib [19]	NR	NR	NR	NR	Lapatinib plus capecitabine
					● 1.5% (grade 2)
					● 0.5% (grade 3/4)
					Lapatinib plus letrozole
					● 4.0% (grade 1/2)
					● 0.9% (grade 3/4)
Nilotinib [18]	10 ^a	2 ^a			NR
	11 ^a	<1 ^a			
Pazopanib [20]	42	7 (grade 3)	6	0	● 8% (treatment) vs. 4% (placebo)
	40	4 (grade 3)	10	0	● 11% (treatment) vs. 5% (placebo) ^b
Sorafenib [21]	9	4 (grade 3)	4	1 (grade 3)	NR
	17	3 (grade 3)	2	<1 (grade 3)	
		<1 (grade 4)			
Sunitinib [17]	34	13 (grade 3)			● 11% (overall with treatment); 1% (grade 3/4) vs. 3% (overall with placebo); 0% (grade 3/4)
	27	10 (grade 3)	5	1 (grade 3)	
	15	4	5	1	● 27% (overall with treatment) ^{a,c}
Vandetanib [16]	33	9	5	1	NR
Monoclonal antibodies					
Bevacizumab [23]	Range: 5–18 ^a				≥Grade 3 LV dysfunction
					1.0% (treatment) vs. 0.6% (placebo)
Trastuzumab [24, 25]	4 [24]		2 [24]		Adjuvant trastuzumab [25]
					● CHF (grade 3/4):
					→ 2.0% (AC-T plus trastuzumab)
					→ 0.4% (TC plus trastuzumab)
					● Reduced LVEF:
					→ 18.6% (AC-T plus trastuzumab)
					→ 9.4% (TC plus trastuzumab)
QT prolongation					
Small-molecule TKIs					
Cabozantinib [22]	A mean increase of QTcF of 10–15 ms was observed at 4 wk after treatment initiation. A concentration-QTc relationship was not established. There were no cabozantinib-treated patients with QTcF >500 ms.				
Lapatinib [19]	QT prolongation was observed in an uncontrolled, open-label, dose-escalation study of lapatinib in advanced cancer patients. Analysis of the data suggested a consistent concentration-dependent increase in QTc interval.				
Nilotinib [18]	QT prolongation was performed in a concentration-dependent manner, and sudden deaths were reported. Increase of QTcF >60 ms from baseline was observed in 4.1% of patients, and QTcF of >500 ms was observed in <1% of patients.				
Pazopanib [20]	In one trial, QT prolongation (≥500 ms) was identified on routine ECG monitoring in 2% of patients. Torsades de pointes occurred in <1% of patients. In two randomized trials, 1% and 0.2% of patients had postbaseline values of 500–549 ms.				
Sorafenib [21]	QT prolongation can occur. No large changes in the mean QTc intervals (i.e., >20 ms) from baseline were detected.				
Sunitinib [17]	Dose-dependent prolongation of QT interval was observed. Torsade de pointes has been observed in <0.1% of patients.				
Vandetanib [16]	Dose-dependent prolongation of QT interval was observed. Torsades de pointes and sudden death have been reported.				
	Frequency of QT prolongation vs. placebo: 14% (grade 3/4: 8%) vs. 1% (grade 3/4: 1%); of the group with QT prolongation, 7% had QTcF >500 ms (~1% overall).				
Monoclonal antibodies					
Bevacizumab [23]	NR				
Trastuzumab [24]	NR				

QT is the duration of ventricular depolarization and repolarization.

^aNo placebo reported.

^bIn patients with baseline and follow-up LVEF measurements.

^c7% experiencing reductions in LVEF to >20% below baseline and to below 50%. In another study, 2% of patients receiving sunitinib experienced cardiac failure leading to death.

Abbreviations: AC-T, anthracycline/cyclophosphamide followed by taxane; AE, adverse event; CHF, congestive heart failure; ECG, electrocardiogram; LV, left ventricular; LVEF, left-ventricular ejection fraction; NR, not reported; QTc, corrected QT interval; QTcF, corrected QT interval using Fridericia's formula; TC, docetaxel/carboplatin; TKI, tyrosine kinase inhibitor.

vascular resistance secondary to endothelial cell damage and dysfunction [28–31]. These effects of VSP inhibitors may be mediated by inhibiting the target receptor in another tissue or by inhibiting additional kinases in a different tissue [32].

Hypertension associated with TKIs is commonly quite manageable with appropriate therapy, and early intervention is key to minimizing additional CV AEs such as heart failure. The Angiogenesis Task Force of the NCI Investigational Drug Steering Committee has issued the following recommendations for the prevention and management of hypertension in patients receiving VSP inhibitors [10]:

- Assess pretreatment risk with a minimum of two standardized BP measurements, a thorough patient history, physical examination, and laboratory evaluation to determine specific CV risk factors.
- Set a goal BP <140/90 mmHg for most patients, in accordance with recommendations for all adults. Higher-risk patients, including those with diabetes and/or chronic kidney disease, should achieve a lower BP goal (e.g., 130/80 mmHg).
- Actively monitor BP weekly during the first cycle of VSP inhibitor therapy and then at least every 2–3 weeks for the duration of treatment.
- Ensure that patients for whom antihypertensive therapy has already been prescribed are adherent and that therapy has been titrated to effective doses. For newly diagnosed patients with hypertension, therapy should be initiated and titrated to effective doses, ideally, before initiating VSP inhibitor therapy.
- Aggressively manage BP to avoid the development of complications associated with excessive or prolonged BP increases.
- Dose reduction or discontinuation of VSP inhibitor therapy may be considered if BP cannot be controlled; once the desired BP is achieved, VSP inhibitor therapy should be reinstituted at the same or lower dose to achieve maximum efficacy on the tumor.

A number of antihypertensive-agent classes (e.g., thiazide diuretics, beta blockers, dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers) are routinely used in patients treated with VSP inhibitors, and these agents have been specifically prescribed to control hypertension associated with VSP inhibitor therapy [10, 33]. The selection of antihypertensive therapy must be individualized by considering the patient's medical history and the specific properties of different classes of antihypertensive agents [33]. Some classes, for example, may be preferable (e.g., renin-angiotensin or sympathetic system inhibitors) over others to minimize the risk of electrolyte depletion (e.g., thiazide diuretics) and consequent QT prolongation [10].

Heart Failure and LV Systolic Dysfunction

There are not yet enough data from randomized controlled clinical trials to indisputably show that aggressive or effective therapy directed at the prevention of heart failure associated with VSP inhibitor treatment will fundamentally change outcomes. Clinical practice suggests that this is an effective long-

term approach. Along with hypertension, heart failure and LV systolic dysfunction are important considerations with TKIs [9]. Whereas heart failure may not be as acute a concern as hypertension in patients treated with TKIs, awareness of this possibility and approaches to prevent and/or manage heart failure can help patients continue to derive the benefits of long-term TKI therapy [34]. Reports of heart failure as a cardiotoxic effect of small-molecule TKIs have been published [2, 35, 36]. Yet, the molecular basis of this effect and its impact on patients treated with TKIs remain poorly understood [2, 6].

Among the mechanisms of action proposed for TKI-associated CV AEs are on-target toxicities [2]. On-target toxicity, also referred to as “mechanism-based” or “target-related” toxicity, may arise when the specific kinase targeted by the therapy provides an important physiologic function in cardiac tissue in addition to the target tumor tissue [2]. An example of on-target toxicity is the cardiac toxicity that may occur with the monoclonal antibody trastuzumab, a human epidermal growth factor receptor 2 (HER-2) antagonist. Because HER-2 appears to play an important role in the proliferation and survival of cardiomyocytes, systemic administration of trastuzumab results in on-target toxicity by interfering with the HER-2 functioning in cardiac tissue, which manifests as LV systolic dysfunction [2]. Similarly, sunitinib has demonstrated direct cardiotoxic effects, which may in part explain the CV AEs associated with this TKI [36].

The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for the diagnosis and prevention of heart failure in all patients, as well as in patients with cancer who may receive potentially cardiotoxic therapies, stratify heart failure into four stages of progression (Fig. 1) [37]. Stages A and B describe asymptomatic yet high-risk states for heart failure because of hypertension, atherosclerotic disease, cardiotoxic therapy use, or a family history of cardiomyopathy, among other causes (stage A), or in the presence of structural heart disease with previous myocardial infarction, LV remodeling, or asymptomatic valvular disease (stage B) [37]. Stages C and D represent states of symptomatic heart failure in patients with structural heart disease and prior or current symptoms, such as shortness of breath, fatigue, and reduced exercise tolerance (stage C) or refractory heart failure with marked symptoms at rest despite maximal medical intervention (stage D) [37].

The ACC/AHA guidelines advise that patients with cancer who are receiving potentially cardiotoxic therapies should be monitored closely for the development of cardiac dysfunction [37]. These guidelines also note that heart failure should be managed regardless of a patient's cancer status. Although no specific recommendations for patients treated with TKIs are provided in the guidelines, beta blockers and/or angiotensin-converting enzyme inhibitors have been used for the treatment of patients with anthracycline-induced cardiomyopathy, which commonly occurs with varying degrees of tachycardia [38–40]. The ACC/AHA guidelines affirm that heart failure related to chemotherapy often improves with appropriate therapy [37]. Because LV dysfunction caused by chemotherapy is likely to improve through early and appropriate treatment [39], implantable devices should be reserved for patients with persistent LV dysfunction or a

Figure 1. American College of Cardiology and American Heart Association stages in the development of heart failure [37]. Reprinted with permission from Wolters Kluwer Health for Hunt SA, Abraham WT, Chin MH et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009;119:e391–e479.

Abbreviations: ACEI, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; EF, ejection fraction; HF, heart failure; LV, left ventricular; MI, myocardial infarction.

prognosis that allows mortality benefit from device-based treatment.

QT Prolongation

Treatment with many agents, both antiarrhythmic and nonantiarrhythmic, has been implicated in QT prolongation associated with increased risk of “torsades de pointes” and sudden cardiac death [41]. The QT interval recorded on an electrocardiogram (ECG) reflects the total duration of ventricular activation and recovery [5]. Clinical utility of the QT interval to evaluate the risk of cardiac events is imprecise and is limited by the lack of a standardized approach to measurement as well as by inpatient and outpatient variability, along with numerous other factors that reduce its reliability and predictive value in clinical practice [42]. Specifically, measured values of the QT interval are known to vary according to heart rate, preexisting cardiac disease, sex, diurnal effects, autonomic tone, activity levels, food ingestion, and operator-generated factors (e.g., variability in placement of ECG leads, body position, observer readings) and between automated readings and physician readings [5, 42–44]. Several correction formulae have been developed to improve the accuracy of QT measurement with corrected QT (QTc) values (Table 3) [5, 45–49]. Although these formulae and management strategies have helped reduce the confounding factors in the measurement of the QT interval, these approaches have not been validated with respect to clinical outcomes. Furthermore, it is

important to note that the risk of developing life-threatening arrhythmias from QTc prolongation is difficult to quantify [42, 43]. The degree of prolonged QTc interval does not reliably correlate with the incidence of torsades de pointes and sudden death. Longer QT intervals are likely associated with an increased risk of torsades de pointes, although the absolute risk is very small [42].

QTc intervals at the upper limit of normal have been proposed for males (>450 ms) and females (>460 ms), although substantial controversy about “normal” QT and QTc intervals continues [5, 44]. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICHTR) considers QTc prolongation >500 ms (and Δ QT [change from baseline] of >60 ms) to be of particular concern because torsades de pointes rarely occurs when QTc is <500 ms [5, 49]. QT prolongation in pathologic states is well known, and a number of congenital and acquired causes of QT prolongation have been observed (Table 4) [5]. Recognizing that QT prolongation is associated with TKI use requires clinicians to carefully balance the expected benefits of therapy with any potential CV risks.

Although the precise mechanisms by which TKIs prolong the QT interval are unknown, several direct and indirect mechanisms have been proposed [5]. A direct interaction between these agents and the human ether-a-go-go-related gene potassium ion channels, which regulate myocardial repo-

Table 3. QT heart rate correction formulas and associated clinical features [5, 48, 49]

Feature	Population-derived correction formulae				Individualized patient correction formula
	Bazett	Fridericia	Framingham	Hodges	
Formula	$QTc = QT (HR/60)^{1/2} = QT (RR)^{-1/2}$	$QTc = QT (HR/60)^{1/3} = QT (RR)^{-1/3}$	$QTc = QT + 154 (1 - 60 / HR) = QT + 0.154 (1,000 - RR)$	$QTc = QT + 1.75 (HR - 60) = QT + 105 (1 / RR - 1)$	$QTc = QT / RR^a$
Type of formula	Nonlinear	Nonlinear	Linear	Linear	Linear mixed
Use	Most commonly used in clinical practice	Used variably in drug development	Used variably in drug development	Used variably in drug development	Used variably in drug development
Unique limitations	Overcorrects QT at fast HRs; undercorrects QT at low HRs; concerning because torsades de pointes frequently occurs at low HR, and Bazett may not reflect this risk by reporting a smaller QTc	Overcorrects at fast HRs; more accurate with lower HRs	Overcorrects at fast HRs; more accurate with lower HRs Large population-based linear regression formula developed from the Framingham heart study; uncertain validity in other populations	Overcorrects at high HRs; may have the least correlation with HR variability	More suitable in early stage clinical trials where QT interval measurements can be made over a broad range of HRs for each individual patient Requires appropriate positive controls to detect relevant effects on QTc interval
Shared limitations	1. QT does not adapt to changes in HR immediately; more than 2 minutes are needed for QT to adjust to a change in HR QT/RR hysteresis. HR correction needs to be done at steady states, and correction formula ignores the dynamicity of the QT/RR relationship. 2. No studies have investigated the correlation between any of the QTc and patient outcomes.				

QT is the duration of ventricular depolarization and repolarization.

^aCorrection term referring to slope of log-transformed QT versus RR relationship.

Abbreviations: HR, heart rate; QTc, corrected QT interval; RR, duration ventricular cardiac cycle.

Adapted with permission. © 2007 American Society of Clinical Oncology. All rights reserved. Strevel EL, Ing DJ, Siu LL. Molecularly Targeted Oncology Therapeutics and Prolongation of the QT Interval. J Clin Oncol 2007;25:3362–3371. The authors, editors, and ASCO are not responsible for errors or omissions in translations.

Table 4. Causes of QT prolongation [5, 43]

Causes	Examples
Genetic	Congenital long QT syndrome (LQT1, LQT2, and LQT3)
Acquired—cardiac structural	Cardiomyopathy/left ventricular hypertrophy Cardiac ischemia Atrioventricular nodal blockade Sinus node dysfunction Mitral valve prolapse
Acquired—metabolic	Electrolytes Altered oral intake Hypothyroidism
Acquired—drug-induced	Antiarrhythmics (e.g., quinidine, procainamide, amiodarone) Psychotropics (e.g., amitriptyline, desipramine, venlafaxine) Antimicrobials (e.g., clarithromycin, erythromycin, azithromycin) Antihistamines (e.g., terfenadine, astemizole) Other (e.g., domperidone, cisapride, droperidol, felbamate, foscarnet, fosphenytoin, indapamide, moexipril/hydrochlorothiazide, octreotide, ondansetron, quinine, tacrolimus, tamoxifen, vasopressin, and arsenic trioxide)
Acquired—other	Connective tissue disease with anti-R _o /SSA (extractable nuclear antigens) antibody Hypothermia Intracranial disease

QT is the duration of ventricular depolarization and repolarization. Adapted with permission. © 2007 American Society of Clinical Oncology. All rights reserved. Strevel EL, Ing DJ, Siu LL. Molecularly Targeted Oncology Therapeutics and Prolongation of the QT Interval. J Clin Oncol 2007;25:3362–3371. The authors, editors, and ASCO are not responsible for errors or omissions in translations.

larization, has been observed using voltage clamp electrophysiology assessments and radioligand competitive binding assays, and this explanation appears to be the most plausible [5]. Indirect predisposing factors for QT prolongation in pa-

tients with cancer treated with TKIs include intrinsic intrapatient repolarization variability, comorbid disease, and multiple concomitant medications with the potential for drug-drug interactions as well as other factors such as electrolyte disturbances secondary to decreased oral intake, or severe nausea, vomiting, or diarrhea [5].

Identifying the potential for QT prolongation during the development of new oncology therapies has led to more systematic approaches that assess this potential as early as possible in the drug-development process. The ICHTR provides guidelines for screening new agents that prolong the QTc in-

Although the incidence of drug-induced QTc prolongation is generally low, patients with cancer are at an increased risk for torsades de pointes relative to healthy populations because of underlying disease and treatments. Moreover, unlike patients with less-advanced cancers, patients with advanced disease of poor prognosis may be more willing to accept a risk of torsades de pointes and other treatment-induced toxicities for drugs that prolong survival.

terval by testing a range of doses, including the maximum tolerated dose, on healthy volunteers. Because exposing healthy individuals to high concentrations of TKIs poses an ethical issue because of the potentially toxic effects of these agents, several oncology trials have pursued alternative study designs [5]. The goals of the oncology drug-development process are to identify any potential risks so that they may be appropriately addressed and managed, allowing promising new therapies to proceed, if feasible, through clinical development, as well as to reduce the possibility of a serious issue emerging with postmarketing use [42]. Although the incidence of drug-induced QTc prolongation is generally low, patients with can-

Table 5. Considerations for the monitoring and prevention of tyrosine kinase inhibitor-associated prolonged QT intervals [16, 44, 50, 52, 55–58]

- Treatment with QT-prolonging agents should be avoided in patients with cardiovascular disease and a history of cardiac events, including torsades de pointes, bradyarrhythmias, and heart failure.
- Concomitant treatment with QT-prolonging drugs, including certain antiarrhythmic, antibiotic, and antifungal agents, should be avoided.^a
- All nonessential medications, such as dietary and herbal supplements, should be avoided.
- Treatment should not be started in patients with excessive corrected QT interval prolongation (>500 ms).
- Electrocardiogram monitoring for QT intervals should occur at baseline and frequently thereafter as indicated by the drug's prescribing information.
- Diarrhea may increase QT prolongation risk due to the resulting electrolyte imbalance; therefore, electrolytes should be monitored and diarrhea appropriately managed.
- Potassium and magnesium levels should be monitored and supplemented as needed.
- Tyrosine kinase inhibitor dosage should be modified or reduced following the drug's prescribing information in patients with impaired renal and hepatic function.

^aArizona Center for Education and Research on Therapeutics (<http://www.qtdrugs.org>) provides a comprehensive list of QT-prolonging agents.

cer are at an increased risk for torsades de pointes relative to healthy populations because of underlying disease and treatments. Moreover, unlike patients with less-advanced cancers, patients with advanced disease of poor prognosis may be more willing to accept a risk of torsades de pointes and other treatment-induced toxicities for drugs that prolong survival [42].

Candidates should undergo careful pretreatment risk assessment for a history of QT interval prolongation or other relevant preexisting cardiac disease, use of antiarrhythmia medications, presence of bradycardia, or electrolyte disturbances [16–20]. Electrolyte concentrations (e.g., serum calcium, potassium, and magnesium) should be evaluated, and imbalances should be corrected before initiating TKI therapy [16, 18–20] and monitored routinely with continued therapy [16–18, 20]. The prescribing information of lapatinib [19] and sunitinib [17] recommend consideration of ECG and electrolyte monitoring during treatment, whereas the prescribing information for pazopanib [20], vandetanib [16], and nilotinib [18] recommend baseline and periodic on-treatment ECG and electrolyte monitoring, with vandetanib and nilotinib specifying the need to also monitor after dose adjustments. With TKIs linked to an increased risk of fatal AEs, including sudden death caused by QT prolongation, it is increasingly important to carefully characterize the potential QT-prolonging effects of new TKI drugs [26, 50]. Cardiologists and other health care professionals, such as nurses, clinical pharmacists, and internists, play an important role in this respect as well as in the appropriate diagnosis and monitoring of QT prolongation [44, 50].

Possible drug-drug interactions also must be considered with certain agents that potentially increase plasma concentrations related to strong CYP3A4 inhibitors [17, 18]. Similarly, drug-food interactions must be considered [18]. TKIs should not be used concomitantly with agents known to prolong the QT interval [16, 18] or should be used only when TKI dose reduction and frequent ECG monitoring are considered [16, 19, 20].

Manufacturers have worked closely with the U.S. Food and Drug Administration to develop extensive risk evaluation and mitigation strategies (REMS) for pazopanib [51], nilotinib

[52], sunitinib [53], and vandetanib [54]. It should be noted, however, that both pazopanib and sunitinib have been released from their REMS requirements [51, 53]. Some considerations for the monitoring and prevention of TKI-associated QT prolongation are listed in Table 5 [16, 44, 50, 52, 55–58]. Additional information about these REMS can be obtained from the manufacturers' websites. It remains to be determined how effective these REMs are as well as if and how they influence clinical practice.

CONCLUSION

The goal of TKI treatment is to maximize antitumor effects while minimizing therapy-associated toxicities. Awareness of potential CV AEs, including hypertension, heart failure, LV systolic dysfunction, and QT prolongation, is an important component of optimal TKI use. In addition, CV AEs such as QT prolongation require careful interpretation by clinicians. The risks and benefits of TKIs (including other oncologic drugs) should be carefully discussed with patients, keeping in mind that those with advanced disease or fewer treatment options may be less concerned with potential cardiac safety issues and more interested in drugs that have demonstrated significantly prolonged survival.

Regular monitoring, early recognition, and appropriate intervention can help more patients derive benefit from long-term TKI therapy. Practicing clinicians should consider that increasing collective experience with these agents will lead to further refinements of their use and of the measures by which the CV AEs are evaluated and graded. The updated AE grading scale (CTCAE 4.03), for example, continues to define these events on the basis of one-time measurements. Whether this approach should continue in the future will be a topic of ongoing discussion. The overall expectation is that the oncology and cardiology communities will continue working together to discover the full benefit of this promising form of targeted cancer therapy.

ACKNOWLEDGMENTS

We thank Richa Tiwari, Ph.D., Susan Moench, Ph.D., and Monica Nicosia, Ph.D., employees of SCI Scientific Communications & Information, who provided medical writing support funded by AstraZeneca LP.

AUTHOR CONTRIBUTIONS

Conception/Design: Daniel J. Lenihan, Peter R. Kowey
Provision of study material or patients: Daniel J. Lenihan, Peter R. Kowey
Collection and/or assembly of data: Daniel J. Lenihan, Peter R. Kowey
Data analysis and interpretation: Daniel J. Lenihan, Peter R. Kowey
Manuscript writing: Daniel J. Lenihan, Peter R. Kowey
Final approval of manuscript: Daniel J. Lenihan, Peter R. Kowey

REFERENCES

1. Lenihan DJ. Tyrosine kinase inhibitors: Can promising new therapy associated with cardiac toxicity strengthen the concept of teamwork? *J Clin Oncol* 2008;26:5154–5155.
2. Cheng H, Force T. Why do kinase inhibitors cause cardiotoxicity and what can be done about it? *Prog Cardiovasc Dis* 2010;53:114–120.
3. Chen MH, Kerkela R, Force T. Mechanisms of cardiomyopathy associated with tyrosine kinase inhibitor cancer therapeutics. *Circulation* 2008;118:84–95.
4. Chen MH. Cardiac dysfunction induced by novel targeted anticancer therapy: An emerging issue. *Curr Cardiol Rep* 2009;11:167–174.
5. Strevel EL, Ing DJ, Siu LL. Molecularly targeted oncology therapeutics and prolongation of the QT interval. *J Clin Oncol* 2007;25:3362–3371.
6. Khakoo AY, Yeh ETH. Therapy insight: Management of cardiovascular disease in patients with cancer and cardiac complications of cancer therapy. *Nat Clin Pract Oncol* 2008;5:655–667.
7. Sternberg CN, Davis ID, Mardik J et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase III trial. *J Clin Oncol* 2010;28:1061–1068.
8. Kim TD, le Coutre P, Schwarz M et al. Clinical cardiac safety profile of nilotinib. *Haematologica* 2012;97:883–889.
9. Hossain A, Chen A, Ivy P et al. The importance of clinical grading of heart failure and other cardiac toxicities during chemotherapy: Updating the common terminology criteria for clinical trial reporting. *Heart Fail Clin* 2011;7:373–384.
10. Maitland ML, Bakris GL, Black HR et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. *J Natl Cancer Inst* 2010;102:596–604.
11. National Cancer Institute. Common Terminology Criteria for Adverse Events v 3.0. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf. Accessed May 13, 2013.
12. National Cancer Institute. Common Terminology Criteria for Adverse Events v 4.0. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed May 13, 2013.
13. National Heart Lung and Blood Institute. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). Available at: <http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.htm>. Accessed May 13, 2013.
14. National Heart Lung and Blood Institute. The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8). Available at: <http://www.nhlbi.nih.gov/guidelines/hypertension/jnc8/index.htm>. Accessed May 13, 2013.
15. Schall R, Ring A. Statistical characterization of

QT prolongation. *J Biopharm Stat* 2010;20:543–562.

16. Caprelsa [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2012. Available at: <http://www.astrazeneca-us.com>.

17. Sutent [package insert]. New York, NY: Pfizer Inc; 2012. Available at: <http://www.pfizer.com>.

18. Tasigna [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012. Available at: <http://www.novartis.com>.

19. Tykerb [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2012. Available at: <http://www.gsk.com/>.

20. Votrient [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2012. Available at: <http://www.gsk.com/>.

21. Nexavar [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2011. Available at: <http://www.bayer.com>.

22. Cometriq [package insert]. South San Francisco, CA: Exelixis, Inc.; 2012. Available at: <http://www.exelixis.com/>.

23. Avastin [package insert]. South San Francisco, CA: Genentech, Inc.; 2012. Available at: <http://www.gene.com/>.

24. Herceptin [package insert]. South San Francisco, CA: Genentech, Inc.; 2010. Available at: <http://www.gene.com/>.

25. Slamon D, Eiermann W, Robert N et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;365:1273–1283.

26. Schutz FA, Je Y, Richards CJ et al. Meta-analysis of randomized controlled trials for the incidence and risk of treatment-related mortality in patients with cancer treated with vascular endothelial growth factor tyrosine kinase inhibitors. *J Clin Oncol* 2012;30:871–877.

27. Neufeld G, Cohen T, Gengrinovitch S et al. Vascular endothelial growth factor (VEGF) and its receptors. *FASEB J* 1999;13:9–22.

28. Mourad JJ, des Guetz G, Debbabi H et al. Blood pressure rise following angiogenesis inhibition by bevacizumab. A crucial role for microcirculation. *Ann Oncol* 2008;19:927–934.

29. Steeghs N, Gelderblom H, Roodt JO et al. Hypertension and rarefaction during treatment with telatinib, a small molecule angiogenesis inhibitor. *Clin Cancer Res* 2008;14:3470–3476.

30. Facemire CS, Nixon AB, Griffiths R et al. Vascular endothelial growth factor receptor 2 controls blood pressure by regulating nitric oxide synthase expression. *Hypertension* 2009;54:652–658.

31. Veronese ML, Mosenkis A, Flaherty KT et al. Mechanisms of hypertension associated with BAY 43-9006. *J Clin Oncol* 2006;24:1363–1369.

32. Kerkela R, Woulfe KC, Durand J-B et al. Sunitinib-induced cardiotoxicity is mediated by off-target inhibition of AMP-activated protein kinase. *Clin Transl Sci* 2009;2:15–25.

33. Mancia G, De Backer G, Dominiczak A et al.

DISCLOSURES

Daniel J. Lenihan: Roche, Astra Zeneca, Singulex (C/A); Acorda, Inc. (RF);
Peter R. Kowey: Astra Zeneca, Johnson and Johnson, Novartis (H).
 Editor in Chief: Bruce Chabner: Sanofi, Epizyme, PharmaMar, GlaxoSmithKline, Pharmacyclics, Ariad, Pfizer (C/A); Eli Lilly (H); Gilead, Epizyme, Celgene, Exelixis (O)
 (C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007;28:1462–1536.

34. Force T, Kerkela R. Cardiotoxicity of the new cancer therapeutics—mechanisms of, and approaches to, the problem. *Drug Discov Today* 2008;13:778–784.

35. Kerkela R, Grazette L, Yacobi R et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med* 2006;12:908–916.

36. Chu TF, Rupnick MA, Kerkela R et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet* 2007;370:2011–2019.

37. Hunt SA, Abraham WT, Chin MH et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009;119:e391–e479.

38. Kalay N, Basar E, Ozdogru I et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol* 2006;48:2258–2262.

39. Cardinale D, Colombo A, Lamantia G et al. Anthracycline-induced cardiomyopathy: Clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol* 2010;55:213–220.

40. Noori A, Lindenfeld J, Wolfel E et al. Beta-blockade in adriamycin-induced cardiomyopathy. *J Card Fail* 2000;6:115–119.

41. Haverkamp W, Breithardt G, Camm AJ et al. The potential for QT prolongation and pro-arrhythmia by non-anti-arrhythmic drugs: Clinical and regulatory implications. Report on a Policy Conference of the European Society of Cardiology Cardiovasc Res 2000;47:219–233.

42. Brell JM. Prolonged QTc interval in cancer therapeutic drug development: Defining arrhythmic risk in malignancy. *Prog Cardiovasc Dis* 2010;53:164–172.

43. Anderson ME, Al-Khatib SM, Roden DM et al. Cardiac repolarization: Current knowledge, critical gaps, and new approaches to drug development and patient management. *Am Heart J* 2002;144:769–781.

44. Al-Khatib SM, Allen LaPointe NM, Kramer JM et al. What clinicians should know about the QT interval. *JAMA* 2003;289:2120–2127.

45. Taran LM, Szilagyi N. The duration of the electrical systole (Q-T) in acute rheumatic carditis in children. *Am Heart J* 1947;33:14–26.

46. Fridericia LS. The duration of systole in an electrocardiogram in normal humans and in patients with heart disease. 1920. *Ann Noninvasive Electrocardiol* 2003;8:343–351.

47. Sagie A, Larson MG, Goldberg RJ et al. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). *Am J Cardiol* 1992;70:797–801.

48. Desai M, Li L, Desta Z et al. Variability of heart rate correction methods for the QT interval. *Br J Clin Pharmacol* 2003;55:511–517.

49. Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Available at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf>. Accessed May 13, 2013.

50. Drew BJ, Califf RM, Funk M et al. Practice standards for electrocardiographic monitoring in hospital settings: An American Heart Association scientific statement from the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young: Endorsed by the International Society of Computerized Electrocardi-

ology and the American Association of Critical-Care Nurses *Circulation* 2004;110:2721–2746.

51. U.S. Department of Health and Human Services. Votrient (pazopanib) Supplement Approval Release REMS Requirement. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2011/022465s006ltr.pdf. Accessed May 13, 2013.

52. U.S. Food and Drug Administration. Risk Evaluation and Mitigation Strategy (REMS). Tasigna (nilotinib). Available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM217737.pdf>. Accessed May 13, 2013.

53. U.S. Department of Health and Human Services. Sutent (sunitinib) Supplement Approval Release REMS Requirement. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2011/021938s013,s017,s018ltr.pdf. Accessed May 13, 2013.

54. U.S. Food and Drug Administration. Caprelsa (vandetanib) Risk Evaluation and Mitigation Strategy (REMS). Available at: [http://www.fda.gov/downloads/](http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM217737.pdf)

[Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM253441.pdf](http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM253441.pdf). Accessed December 6, 2012.

55. CredibleMeds. Drug Lists by Risk Groups: Drugs that Prolong the QT Interval and/or Induce Torsades de Pointes. Available at: <http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm>. Accessed May 13, 2013.

56. CredibleMeds. Clinically Important Drug Interactions. Available at: <http://www.azcert.org/medical-pros/druginteractions.cfm>. Accessed May 13, 2013.

57. Kubota T, Shimizu W, Kamakura S et al. Hypokalemia-induced long QT syndrome with an underlying novel missense mutation in S4–S5 linker of KCNQ1. *J Cardiovasc Electrophysiol* 2000;11:1048–1054.

58. Kulkarni P, Bhattacharya S, Petros AJ. Torsade de pointes and long QT syndrome following major blood transfusion. *Anaesthesia* 1992;47:125–127.

CME

This article is available for continuing medical education credit at CME.TheOncologist.com.