Cardiovascular Effects of Tyrosine Kinase Inhibitors in Patients With Advanced Renal Cell Carcinoma at the VA San Diego Healthcare System

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Patients who have or are at high risk for developing cardiovascular disease and who are taking tyrosine kinase inhibitors for renal cell carcinoma should receive routine cardiovascular event monitoring during the first 4 months of therapy.

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Targeted therapies have transformed the treatment of many malignant diseases by inhibiting molecular pathways involved in tumor growth and oncogenesis. Although these therapies can prevent disease progression, toxicities often result. Renal cell carcinoma (RCC) is one of many cancers that responds well to these therapies.

RCC accounts for 2% to 3% of all malignancies in adults worldwide. About 30% of patients with RCC present with metastatic or advanced disease.[1] Cytokine therapy was the standard of care until multitargeted tyrosine kinase inhibitors (TKIs) were developed. Over the past 12 years, the US Food and Drug Administration (FDA) has approved 6 TKIs for the treatment of RCC: axitinib, cabozantinib, lenvatinib, pazopanib, sorafenib, and sunitinib. Vascular endothelial growth factor receptor (VEGFR) is one of many tyrosine kinase receptors targeted by these medications. This mechanism prevents angiogenesis and consequently increases the risk for hypertension, bleeding, and clot formation.

Given these risks, many patients were excluded from the initial clinical trials of these medications if they had a history of uncontrolled hypertension, advanced heart failure (HF), or a significant cardiovascular (CV) event within 6 months prior to study enrollment. Many of these studies did not report the incidence of CV events (other than hypertension) that occurred during the early trials.[2] The recommended monitoring for TKI therapies is focused mainly on blood pressure. For patients on pazopanib and sunitinib therapy, baseline and periodic electrocardiograms (ECGs) are recommended; echo-cardiograms are recommended only for patients with a history of cardiac disease.[3,4] In patients on sorafenib therapy, ECG is recommended for those at risk for corrected QT (QTc) interval prolongation.[5]

According to a meta-analysis of the literature published between 1966 and 2013, many studies reported a CV toxicity risk associated with the TKIs used in RCC treatment.[6] However, some studies have found modest, not clinically significant changes in cardiac function in patients with advanced disease. In 2013, Hall and colleagues found 73% of patients they studied experienced some type of CV toxicity, whereas only 33% of patients had CV toxicity when hypertension was excluded.[7] Interestingly, Rini and colleagues found that RCC patients receiving sunitinib had better response rates and progression-free survival when they developed hypertension compared with those who did not develop hypertension.[8]

A review of several studies revealed similar numbers in patients on TKI therapy presenting with symptomatic HF, but Hall and colleagues found that 27% of patients developed asymptomatic left ventricular dysfunction.[7,9,10] These results suggest routine monitoring may allow for appropriate preventive interventions. In patients receiving TKI therapy, CV events, including QTc prolongation, left ventricular HF, myocardial infarction (MI), hypertension, pulmonary hypertension, and stroke, were commonly reported by investigators.[7,9,10] Currently, there are no studies of the incidence of CV events for the 5 TKIs (axitinib, cabozantinib, pazopanib, sorafenib, sunitinib) in this patient population.

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TABLE 1

Baseline Patient Characteristics

Characteristics	Tyrosine Kinase Inhibitor					
	All	Axitinib	Cabozantinib	Pazopanib	Sorafenib	Sunitinib
Patients, No.	54	6	1	11	13	23
Median age, y	66	66	60	65	66	67
Median body mass index	23.2	19.6	33.2	25.4	22.2	23.5
Male gender, No.	50	5	1	10	12	22
Race/ethnicity, No.						
White	46	6	1	10	11	18
African American	2	0	0	1	0	1
Native American	1	0	0	0	0	1
Not Hispanic or Latino	5	0	0	0	2	3
Tobacco use, No.						
Former smoker	27	4	0	7	6	10
Active smoker	9	0	0	1	3	5
Never smoker	16	1	1	3	3	8
ECOG-PS, No.						
0	6	0	0	1	2	3
1	20	3	0	7	4	6
1-2	3	1	0	0	0	2
2	9	0	0	2	2	5
2-3	5	1	1	0	1	2
Unknown	11	1	0	1	4	5
Treatment duration, No.						
< 6 mo	29	2	1	9	6	11
6-12 mo	18	3	0	2	6	7
> 12 mo	7	1	0	0	1	5
History of cardiac disease or comorbidity, No.						
Total	45	5	1	10	11	18
Hypertension	43	5	1	10	11	16
Congestive heart failure	5	1	0	0	2	2
MI/coronary artery bypass grafting	8	2	0	1	3	2
Coronary artery disease	16	2	0	3	6	5
Unstable angina	1	0	0	1	0	0
Atrial fibrillation/atrial flutter	1	0	0	0	1	0
Heart block	3	0	0	1	1	1
Stroke	3	0	0	1	1	1
Hyperlipidemia	17	2	0	7	3	5
Diabetes mellitus	17	1	0	4	5	7
CKD/end-stage renal disease	5	0	0	1	3	1
None	9	1	0	1	2	5

Abbreviations: CKD, chronic kidney disease; ECOG-PS, Eastern Cooperative Oncology Group performance status; MI, myocardial infarction.

TKI therapy may require cardiac monitoring of all patients, as studies have associated TKIs with CV toxicity in varying degrees. Therefore, the authors set out to determine the incidence of CV events as well as time to first CV event in patients with and without a history of CV disease (CVD) who received a TKI for advanced RCC. More frequent monitoring for CV toxicity may present opportunities for clinical interventions for all patients on TKI therapy—especially for those with HF or other diseases in which the goal of therapy is to prevent disease progression. As TKIs have emerged as the standard treatment option for advanced RCC, many patients will continue therapy until disease progression or intolerable toxicity. Identifying and using appropriate monitoring parameters can lead to preventive interventions that allow patients to benefit from TKI therapy longer. At the US Department of Veterans Affairs (VA) San

TABLE 2

Cardiovascular Event Rates

Event, No. (%)	Tyrosine Kinase Inhibitor			
	All (n = 45)	Sunitinib (n = 18)	Sorafenib (n = 11)	Pazopanib (n = 10)
Any	11 (24)	5 (28)	4 (36)	2 (2)
Hypertension	6 (13)	3 (17)	2 (18)	1 (1)
Myocardial infarction	2 (4)	2 (11)	—	—
Congestive heart failure	1 (2)	—	—	1 (1)
QTc prolongation	1 (2)	—	1 (9)	—
Stroke	1 (2)	—	1 (9)	—
History of cardiovascular disease, n Yes No P	 11 0 .18	 5 0 .76	 4 0 .46	 2 0 .99

Abbreviation: QTc, corrected QT interval.

Diego Healthcare System (VASDHS), patients undergo routine cardiac monitoring at the discretion of the provider.

In this retrospective study, the authors wanted to determine the incidence of CV events in patients with and without a history of CVD who were receiving TKIs for advanced RCC. The authors also wanted to evaluate time to CV event from start of therapy in order to determine how often monitoring may be needed. The outcomes of this study may lead to a change in practice and development of monitoring parameters to ensure appropriate and adequate management of TKI therapy in RCC.

METHODS

Each year, the VASDHS oncology team diagnose 5 to 10 patients with RCC who begin TKI therapy. When sorafenib was approved by the FDA in 2005, VASDHS estimated that about 100 of its patients had an RCC diagnosis and would be treated with a TKI between December 2005 and July 2017.

The authors identified VASDHS patients with a diagnosis of advanced RCC who received axitinib, cabozantinib, pazopanib, sorafenib, or sunitinib between December 1, 2005 and July 31, 2017. Patients were included if they had been on therapy for at least 30 days. The VASDHS pharmacy informatics team assisted in extracting a list of patients with an ICD-9 or ICD-10 diagnosis of RCC and using prescription fills for any of the 5 TKIs previously noted. Medical records were reviewed for frequency of prescription fills, age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, TKI treatment duration, previous history of CVD, ethnicity, and smoking status. If documented, the incidence of CV events was reviewed for each patient at 0, 1, 3, 6, and 12 months. Patients who received medications (Appendix) for their CVD were assessed for adherence based on history of prescription refills from their medical records. Adherence was evaluated for the duration that patients were concurrently taking an oral TKI. The institutional review board at VASDHS approved the study design.

All patients included in this study started TKI therapy since the December 2005 FDA approval of sorafenib, the first oral TKI for treatment of RCC. Each new start was recorded as a separate event, regardless of previous oral TKI therapy. Albiges and colleagues found that the approximate median time from starting TKI therapy to complete response was 12.6 months, and the median duration of TKI therapy after complete response was 10.3 months.[11] Based on these results, the follow-up period for patients in this study was 2 years after the start of each TKI therapy. For data analysis, patients were stratified by CVD history (yes or no). In addition, composite outcomes were evaluated to identify a potential cumulative increased risk for CV events for patients who had been on multiple TKI therapies.

For this study, CV toxicities were characterized using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03; severity of adverse events (AEs) was graded 1 to 5. CTCAE commonly has been used to assess AEs in oncology clinical trials. The CV AEs selected for this study included QTc prolongation, hypertension, left ventricular dysfunction, stroke, myocardial infarction (MI), and pulmonary arterial hypertension. CTCAE was not used to assess left ventricular dysfunction, as the rating is based on symptomology. Instead, worsening left ventricular ejection fraction (LVEF) was based on comparisons of ECG results at baseline with results at 1, 3, 6, and 12 months. A normal ECG result was defined as no structural change in the left ventricle, or LVEF $\geq$ 55%, and an abnormal result was defined as structural changes in the left

FIGURE 1
Time to Cardiovascular Events Based on Therapy
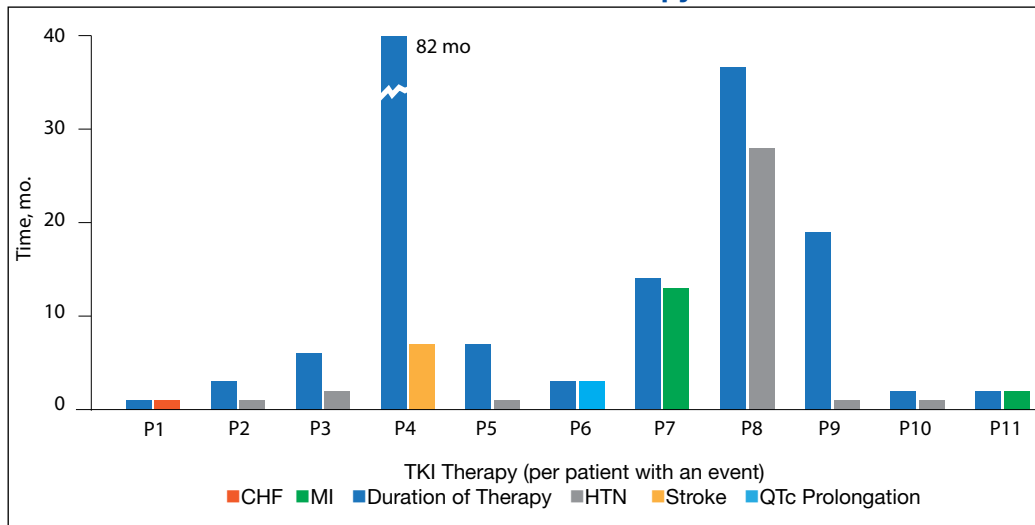
P1 and P2 were prescribed pazopanib, P3-P6 were prescribed sorafenib, and P7-P11 were prescribed sunitinib.
Abbreviations: CHF, congestive heart failure; HTN, hypertension; MI, myocardial infarction; P, patient; QTc, corrected QT interval; TKI, tyrosine kinase inhibitor.

ventricle, or LVEF < 55%. Given updates in blood pressure (BP) guidelines and uncertainty regarding the clinical utility of prehypertension, grade 1 hypertension was excluded as an AE.

Primary outcomes included incidence of CV events and time to first CV event after initiation of TKI therapy. Secondary outcomes included changes in ECG or echocardiogram results at 0, 1, 3, 6, and 12 months. Secondary outcomes at scheduled time points were not readily available for every patient, but any available time points were gathered to aid in identifying an optimal period for cardiac monitoring. In addition, patients with a history of CVD were evaluated for adherence to common first-line therapies for each disease.

A Fischer exact test was used to compare the incidence of CV events in patients with and without a history of CVD (significance level, $\alpha = 0.05$). A subgroup analysis was used to compare the incidence of CV events in patients who experienced a CV event (significance level, $\alpha = 0.05$). A Kaplan-Meier survival curve was used to determine time to first CV event. A log-rank test with significance level set at $\alpha = 0.05$ also was used.

RESULTS
An initial database search identified 134 patients who received TKI therapy at VASDHS between December 1, 2005 and July 31, 2017. According to retrospective chart review, 54 patients met the inclusion criteria for the study (Table 1).

Patients without a history of CVD (17%) did not experience any CV events while on TKI

TABLE 3
Study Patients With Documented Cardiac Monitoring (No.)

	Baseline	1 mo	3 mo	6 mo	12 mo
Electrocardiogram					
Normal: QTc < 450 ms, or no electrocardiographic changes	25	7	6	9	8
Abnormal: QTc > 450 ms, or ST-segment elevation or depression	8	5	2	5	4
Echocardiogram					
Normal: no structural change, or LVEF > 55%	11	1	1	1	0
Abnormal: structural changes in left ventricle, or LVEF < 55%	2	1	0	0	1

Abbreviations: LVEF, left ventricular ejection fraction; QTc, corrected QT interval.

Incidence of Cardiovascular Events Among Tyrosine Kinase Inhibitors
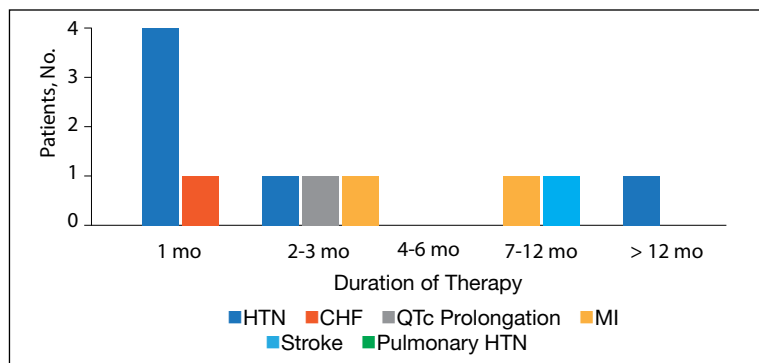
Abbreviations: CHF, congestive heart failure; HTN, hypertension; MI, myocardial infarction; QTc, corrected QT interval.

therapy. Of the patients with a history of CVD, 9 (20%) experienced ≥ 1 CV event. Fifty-five percent of the events experienced were hypertension. One patient experienced QTc prolongation, and 2 patients experienced MI. As already noted, each new start of TKI was recorded as a separate event, regardless of previous TKI therapy. Among patients with a history of CVD, 2 experienced 2 CV events. Overall, 11 CV events occurred among patients who received ≥ 1 TKI, corresponding to an overall incidence of 24% (Table 2). Most CV events occurred within the first 6 months of therapy, with median time to first CV event of 2 months (Figures 1 and 2). Median duration of therapy for these patients was 6 months. All CV events occurred within the first year of therapy (Figures 3 and 4), except for 1 event that occurred at 28 months. A review of the charts of the 11 patients who experienced a CV event revealed that 1 patient was adherent to prior CV therapy, 5 patients were not adherent, and 5 patients had not been on any prior CV therapy.

Of the 13 patients who were exposed to ≥ 2 TKI therapies, 2 experienced a CV event. Both patients were started on sunitinib and were switched to sorafenib. One of these used sunitinib for 7 months, experienced a partial response and was switched to sorafenib (with a 3-month break between therapies). The second patient was on sunitinib for 24 months, with multiple doses held because of low blood counts and diarrhea. While on sunitinib, this patient experienced a HF exacerbation, determined to be caused by the underlying disease. This event occurred 17 months after sunitinib was started, and therapy was continued for another

7 months. The patient was switched to sorafenib because of poor tolerability and disease progression. While on sorafenib, this patient experienced grade 1 QTc prolongation.

DISCUSSION

Of the available oral TKI therapies for RCC, sunitinib and sorafenib have the most data associated with nonhypertensive CV toxicity.[2,7-10,12] In studies, the percentage of patients who experienced CV toxicity while on sunitinib or sorafenib has ranged widely, from 2.7% to 33.8%; the variance may be attributable to differences in how institutions report CV toxicities.[7-9]

According to the prescribing information for TKIs, hypertension is frequently reported as an AE for all 5 TKIs, and BP monitoring is recommended.[3,4] However, the development of hypertension with these TKIs has been associated with response to therapy.[7] With pazopanib, sorafenib, and sunitinib, there is a higher incidence of other AEs: edema, HF, MI, and QTc prolongation. Baseline ECG is recommended for all patients started on pazopanib and sunitinib and for patients with a history of CVD who are started on sorafenib. An ECG is recommended for patients with a history of CVD who are started on pazopanib and sunitinib.

Even with the medication prescribing information recommendations, it is unclear how frequently patients should be monitored. At VASDHS, CV monitoring for any patient started on a TKI remains at the discretion of the oncologist. There are concerns that ordering cardiac monitoring tests, which might be unnecessary, will change or guide therapy. In this study, data evaluation revealed 1 patient who experienced a CV event had a CVD history that was not documented in the patient's medical history. It is important that providers obtain a detailed clinical assessment of patients CV history during each visit to determine whether CV monitoring should be considered. Patients also may benefit from additional counseling to emphasize the importance of adherence to CV medication therapy to reduce the incidence of these events.

Data from this study indicate that routine CV monitoring should be considered in patients with CVD, in keeping with current medication prescribing information recommendations. Of the patients who had a CV event, 54% experienced hypertension, 18% MI, and 28% stroke, QTc prolongation, or congestive HF. All these patients had a history of CVD, but many did not

FIGURE 3
Time to First Cardiovascular Event of Any TKI Therapy
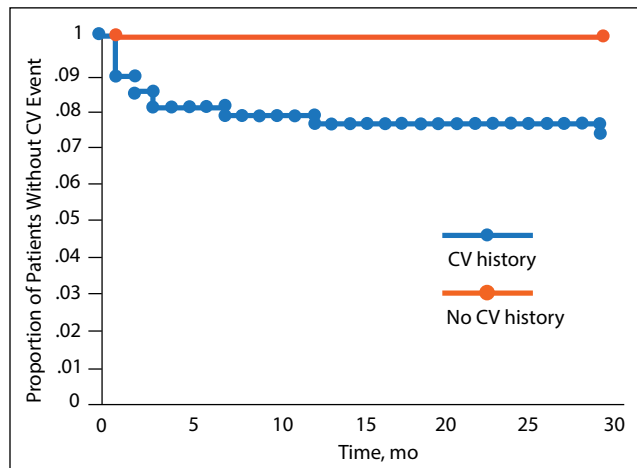
Abbreviations: CV, cardiovascular; TKI, tyrosine kinase inhibitor.

FIGURE 4
Time to First Cardiovascular Event of Any TKI Therapy at 12 Months
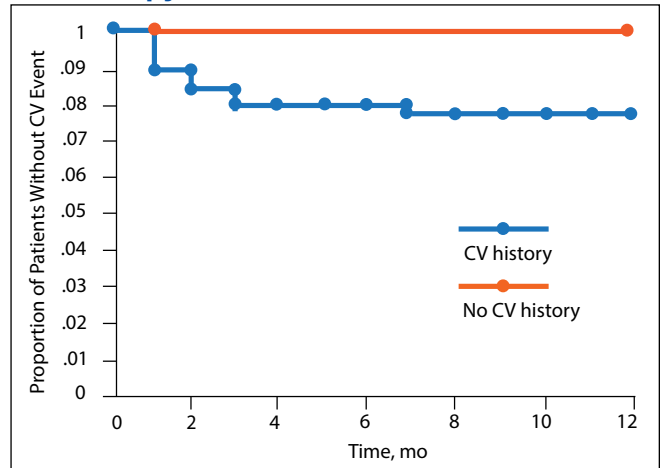
Abbreviations: CV, cardiovascular; TKI, tyrosine kinase inhibitor.

undergo baseline CV monitoring (Table 3) at the start of therapy. Thus, it was difficult to determine whether these patients' CV events could have been prevented with baseline monitoring. However, baseline and routine cardiac monitoring within the first 4 months of therapy may help identify worsening CV function.

Limitations

This retrospective study had several limitations. Many patients did not have a baseline cardiac monitoring test or any monitoring during therapy. Often, a cardiac test was performed only when the patient was symptomatic or experiencing a CV event. In addition, because of intolerance or nonadherence to therapy, many patients discontinued treatment early, before completing 30 days. That axitinib and cabozantinib are newer therapies and not first-line at VASDHS during the data collection period accounts for the small number of patients on these therapies. Therapy was shorter for patients started on pazopanib, axitinib, and cabozantinib than it was for patients on sunitinib and sorafenib. Duration of therapy may affect treatment-related events, but the majority of patients in this study experienced an event within 4 months of therapy. About half of the patients who experienced an event were nonadherent to their CV medication regimen. Another potential limitation is that this study was conducted at VASDHS, where most patients are male (RCC incidence is 2:1 male:female).

CONCLUSION

In this study, CV events occurred in 24% of patients with a history of CVD; 11% of these events were nonhypertensive. Baseline cardiac monitoring was not performed for most patients started on TKI therapy, but tests were performed once patients became symptomatic. The study results suggest that high-risk patients should undergo routine cardiac monitoring during the first 4 months of TKI therapy, in keeping with medication package insert monitoring recommendations. Cardiac monitoring of high-risk patients will allow for earlier identification of cardiac decline and offer opportunities for interventions, such as pharmacist-driven protocols to start CV medications. Implementation of this study's recommendations should be evaluated to determine whether outcomes improve with routine cardiac monitoring in these high-risk patients.

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APPENDIX
Cardiovascular Maintenance Medications of Study Patients

Hypertension[13]	Left Ventricular Dysfunction[14]	Stroke[15]	Myocardial Infarction[16,17]	Pulmonary Arterial Hypertension[18]
ACEI (eg, benazepril, captopril, enalapril, lisinopril) ARB (eg, losartan)	ACEI (eg, benazepril, captopril, enalapril, lisinopril) ARB (eg, losartan) ARNI (eg, sacubitril/valsartan)	Aspirin	ACEI (eg, benazepril, captopril, enalapril, lisinopril) ARB (eg, losartan)	Prostacyclin analogue (eg, epoprostenol, treprostinil)
β-blocker (eg, bisoprolol, carvedilol, metoprolol)	β-blocker (eg, bisoprolol, carvedilol, metoprolol)	Antiplatelet (eg, clopidogrel)	β-blocker (eg, bisoprolol, carvedilol, metoprolol)	Endothelin receptor antagonist (eg, ambrisentan, bosentan)
Aldosterone antagonist (eg, spironolactone)	Aldosterone antagonist (eg, spironolactone)	Statin (eg, atorvastatin, rosuvastatin)	Aspirin	Phosphodiesterase inhibitor (eg, sildenafil, tadalafil)
Calcium channel blocker (eg, amlodipine, diltiazem, verapamil)	Loop diuretic (eg, bumetanide, furosemide)		Antiplatelet (eg, clopidogrel, prasugrel, ticagrelor)	Riociguat
Thiazide diuretic (eg, hydrochlorothiazide)	Isosorbide dinitrate, hydralazine		Statin (eg, atorvastatin, rosuvastatin)	Selexipag

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor blocker and neprilysin inhibitor.