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Prospective Evaluation of Sunitinib-Induced Cardiotoxicity in Patients with Metastatic Renal Cell Carcinoma

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Abstract

Purpose: To prospectively evaluate cardiotoxicity risk with sunitinib in metastatic renal cell carcinoma (mRCC) routine clinical practice using comprehensive echocardiography and biomarker phenotyping.

Experimental Design: In a multicenter prospective study of 90 patients with mRCC, echocardiography and biomarkers of cardiovascular injury and stress were quantified at baseline, 3.5, 15, and 33 weeks following sunitinib initiation. These "on-drug" visits corresponded to cycles 1, 3, and 6, respectively. Left ventricular (LV) dysfunction was defined as an absolute decline in LV ejection fraction (LVEF) by $\geq$10% to a value of <50%. Conditional survival analyses predicted the risk of LV dysfunction. Linear mixed-effects models estimated changes in LVEF, high-sensitivity Troponin I (hsTnI), and B-type natriuretic peptide (BNP) over time.

Results: The predicted risk of LV dysfunction by cycle 6 was 9.7% (95% confidence interval, 3%–17%). The majority of events occurred in the first treatment cycle. This risk diminished to 5% and 2% in patients who had not experienced dysfunction by the completion of cycles 1 and 3, respectively. All evaluable patients who experienced LV dysfunction had subsequent improvement in LVEF with careful management. Six patients (6.7%) developed hsTnI elevations >21.5 pg/mL, and 11 additional patients (12.2%) developed BNP elevations >100 pg/mL. These elevations similarly tended to occur early and resolved over time.

Conclusions: On average, patients with mRCC receiving sunitinib exhibit modest declines in LVEF and nonsignificant changes in hsTnI and BNP. However, approximately 9.7% to 18.9% of patients develop more substantive abnormalities. These changes occur early and are largely recoverable with careful management.
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Introduction

Numerous therapies targeting the VEGF molecular pathway have been approved for the treatment of metastatic renal cell carcinoma (mRCC) (1–5). The availability of such therapies has resulted in a doubling of the median overall survival to approximately 2 years, and VEGF-directed therapies remain the current standard of care for frontline mRCC management. Sunitinib is a multitargeted VEGF receptor tyrosine kinase inhibitor (TKI) and is a standard first-line treatment option for mRCC (6). Indeed, a recent review of treatment practices at U.S. community oncology practices indicated that sunitinib was the preferred initial therapeutic option for mRCC management (7).

Although sunitinib and other VEGF-directed therapies have significantly improved clinical outcomes for patients with mRCC, they have also been associated with several cardiovascular toxicities, including hypertension, left ventricular (LV) dysfunction, and heart failure (8–10). While the exact mechanisms for cardiotoxicity remain unclear, VEGF signaling is known to play an important role in maintaining cardiac function and homeostasis in both ischemic and nonischemic cardiomyopathy (11–13). In addition, as a multitargeted kinase inhibitor, sunitinib has effects on the AMP-activated protein kinase (AMPK) and platelet-derived growth factor receptor (PDGFR), which are critical for cardiomyocyte function and survival (11, 12). Finally, an increase in systemic arterial load may result from a reduction in vasodilatory nitric oxide production and from vascular rarefaction, and may further adversely affect LV systolic function (14, 15).

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Translational Relevance

This is the first multicenter, prospective study of sunitinib-induced cardiotoxicity in patients with metastatic renal cell carcinoma (mRCC) using precise and standardized cardiac imaging and biomarker assessments. Our results demonstrate that on average, patients with mRCC receiving sunitinib exhibit modest declines in left ventricular ejection fraction (LVEF) and nonsignificant changes in high-sensitivity Troponin I (hsTnI) and B-type natriuretic peptide (BNP) over time. LV dysfunction, as defined by LVEF declines of $\geq$10% to <50%, occurred in 9.7% of patients. Similarly, incident increases in hsTnI to >21.5 pg/mL or BNP to >100 pg/mL occurred in a total of 18.9% of patients (6.7% and 12.2% for hsTnI and BNP, respectively). LVEF declines and biomarker increases occurred early and were not sustained. These findings provide prospective evidence to guide strategies for cardiotoxicity monitoring with sunitinib therapy.

However, our understanding of sunitinib-related cardiotoxicity and its clinical significance in patients with mRCC remains limited and is largely defined by retrospective analyses in clinical trial populations. In a meta-analysis of mostly phase II and III clinical trials in a variety of advanced solid tumors, the overall incidence of heart failure in patients treated with sunitinib was estimated to be 4.1% (16). Several retrospective studies performed in a variety of treatment settings have reported that the incidence of sunitinib-induced cardiotoxicity specifically in patients with mRCC ranges from approximately 3% to 30% (17–20). The clinical interpretation of these varied findings has been further limited by the use of nonstandardized cardiac monitoring protocols, varying definitions of cardiotoxicity, including composites of LV ejection fraction (LVEF) decline and nonspecific heart failure symptoms, and a lack of quantitative or core laboratory assessment of these measures. As a result, there is little consensus regarding recommended cardiac toxicity monitoring strategies in the setting of mRCC and sunitinib therapy (6). This has the potential to be of significant impact given the prospect for expanding indications for sunitinib use, particularly in the adjuvant treatment setting.

Given the therapeutic importance of VEGF receptor TKIs, it is critical to better understand the treatment-related cardiovascular risk in the general mRCC patient population in order to guide effective cardioprotective monitoring. As such, we performed a multicenter prospective cohort study to precisely define the longitudinal changes in cardiac function that occur in a real-world cohort of patients with mRCC newly initiated on sunitinib therapy. In particular, we aimed to define the risk of sunitinib-induced subclinical cardiac injury through detailed quantitative assessment of both cardiac function by echocardiography, and myocardial injury and stress by cardiac biomarkers, including high-sensitivity Troponin I (hsTnI) and B-type natriuretic peptide (BNP).

Patients and Methods

Study design

This was a multicenter prospective cohort study performed at five academic medical centers, including the University of Pennsylvania, the Vanderbilt University Medical Center, the University of Wisconsin, University Hospitals Case Medical Center, and the University of Utah. Eligible participants were accrued between December 2011 and December 2015 and included patients with mRCC who were planned to initiate sunitinib therapy. Sunitinib starting dose, schedule, and dose adjustments were determined at the discretion of the treating medical oncologist. All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board at each individual participating site.

Prior to the initiation of sunitinib, enrolled participants underwent a detailed review of their medical history, including prior cardiac events, cardiovascular risk factors, and current medications, with all findings verified by the oncology provider. Cardiac symptoms were assessed using the MD Anderson Symptom Inventory–Heart Failure (MDASI-HF) survey, which records heart failure symptoms on a scale of 0 to 10 (21). In addition, all participants underwent a baseline transthoracic echocardiogram, blood pressure assessment, and blood sample collection. Study follow-up was designed to detect both the peak and late incidences of LV dysfunction as a result of sunitinib exposure (18). As such, follow-up echocardiograms, plasma biomarkers, and clinical assessments (including cardiac history, symptom assessment, blood pressure measurement, and cardiac medication use) were performed during follow-up visits at 3.5 weeks ($\pm$1 week), 15 weeks ($\pm$2 weeks), and 33 weeks ($\pm$2 weeks) after the initiation of sunitinib (Fig. 1). These follow-up visits were timed to coincide with sunitinib exposure during cycles 1, 3, and 6 of therapy, respectively, and were scheduled at a time when the participant would be actively taking sunitinib (i.e., "on drug"). The decision to initiate antihypertensive or other cardiovascular medications was at the discretion of the treating medical provider. In the event of sunitinib discontinuation due to disease progression or intolerable toxicity, follow-up cardiac assessment was obtained per protocol.

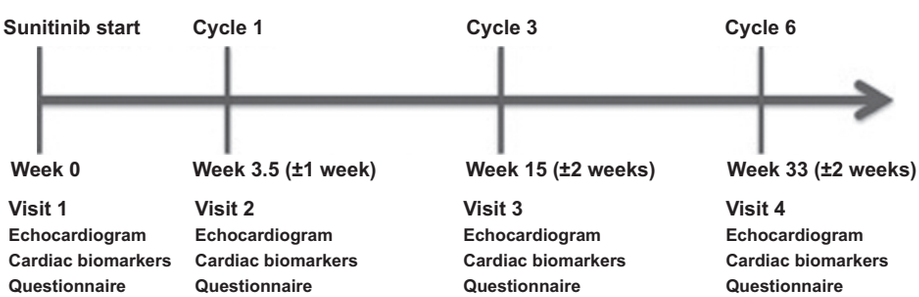

Figure 1.
Study schema. Protocol-specified cardiac assessments timed to coincide with sunitinib exposure during cycles 1, 3, and 6 of therapy.

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Echocardiography quantitation and definition of LV dysfunction

Transthoracic echocardiograms were performed at the participating sites according to a standardized protocol. Two-dimensional images were acquired using Philips IE33 machines. Echocardiography quantitation was independently performed in the imaging core laboratory at the Hospital of the University of Pennsylvania by trained sonographers blinded to all patient characteristics. Quantitation of end-systolic and end-diastolic LV volumes was performed using TomTec Image Arena (TomTec Imaging Systems). LVEF was derived from the stroke volume (defined as the difference between end-diastolic and end-systolic volumes), divided by the end-diastolic volume (22). LV dysfunction was defined as an absolute decline in the LVEF by $\geq$10% to a resultant value of <50% (23–26).

Biomarker analyses

Plasma samples were collected in EDTA tubes, processed at 3353 RPM for 20 minutes at room temperature, aliquoted, and stored at −80°C until the time of assay. hsTnI and BNP were quantitatively measured using the Singulex Single Molecule Counting laboratory assay (27). Elevations in hsTnI > 99th percentile for a population with, or at risk for, comorbid cardiovascular disease (>21.5 pg/mL), or elevations in BNP to >100 pg/mL were considered abnormal (27). hsTnI or BNP was missing for 13 of the 281 (4.6%) protocol-defined biomarker assessments.

Statistical analysis

Participants were eligible for analysis if they received sunitinib therapy and underwent at least a baseline echocardiogram and clinical assessment. Descriptive statistics for key demographic and clinical variables were performed. The Kaplan–Meier method was used to analyze the time-to-event endpoints of mRCC-specific survival, time to discontinuation of sunitinib, and time to incident LV dysfunction. Participants who did not experience an event of interest were censored at the date of last follow-up. Individual linear mixed-effects models with a random intercept to account for intraparticipant correlation of repeated measures were used to estimate LVEF, hsTnI, or BNP changes over time. Linear regression models adjusted for baseline LVEF were also used to estimate the associations between individual baseline factors or biomarkers (hsTnI or BNP) and changes in LVEF. Baseline clinical characteristics selected *a priori* for univariable analyses included age, sex, body mass index (BMI), cardiac medication use, sunitinib starting dose, systolic blood pressure, pulse pressure, and history of hypertension or hyperlipidemia. Similarly, univariate linear models were used to evaluate the association between changes in cardiac symptoms and changes in LVEF. Specific cardiac symptoms included the change in dyspnea severity and change in the MDASI-HF score (average response for 8 heart failure symptoms: severity of ankle edema, abdominal bloating, sudden weight gain, lack of energy, orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough, and palpitations) (21). Finally, in order to determine the predicted risk of LV dysfunction over time, unadjusted conditional survival analyses were used to estimate the risk of LV dysfunction prior to 33 weeks of sunitinib therapy (cycle 6). Here, the predicted risk was derived conditional on "surviving" without LV dysfunction at either 6 weeks or 18 weeks of sunitinib therapy (completion of cycles 1 or 3, respectively). Hypothesis tests were two-sided with a type I error rate of 0.05. All analyses were performed with R statistical software (R Foundation for Statistical Computing).

Results

Study population

A total of 90 participants were eligible for analysis and contributed 281 echocardiograms and 272 biomarker measures over the course of study follow-up. Participant demographic and clinical characteristics are summarized in Table 1. The median age was 63 years [interquartile range (IQR), 55–68]. The majority of participants had clear cell mRCC with a history of prior nephrectomy (78%) and received initial systemic therapy with sunitinib (87% with no prior systemic RCC therapy). Cardiovascular risk factors were highly prevalent at baseline, including hypertension (54%), coronary artery disease (9%), and current/former tobacco use (57%). The median baseline LVEF was 49.8% (IQR, 44.6–54.1), and the median baseline values for hsTnI and BNP were 1.7 pg/mL (IQR, 1.0–3.6) and 32.8 pg/mL (IQR, 16.7–65.4), respectively.

The median study follow-up time was 30.9 weeks (IQR, 6.3–35.0 weeks). Among the five study sites, 49 participants (54%) completed the full protocol-specified follow-up including echocardiograms and cardiac assessments through approximately 33 weeks of study follow-up time. Twenty-one participants (23%) withdrew from the study prior to 33 weeks, and three others (3%) were lost to routine oncologic follow-up. Reasons for early participant withdrawal included disease progression ($N = 16$) and patient preference ($N = 5$). Seventeen participants (19%) died from mRCC during the course of study follow-up, and there were no deaths from other causes (Fig. 2A). Eighty-three participants (92%) and 62 participants (69%) completed follow-up through 3.5 weeks (cycle 1) and 15 weeks (cycle 3), respectively. Participants completing study follow-up had similar baseline characteristics as those participants who did not (Supplementary Table S1). At the end of protocol follow-up (33 weeks, cycle 6), the majority (87%) of evaluable participants active in the study remained on sunitinib therapy. The Kaplan–Meier analysis for time to discontinuation of sunitinib is displayed in Fig. 2B.

Incidence of LV dysfunction and change in incidence over time

Overall, there was a very modest, but statistically significant decline in LVEF of 1.9% [95% confidence interval (CI), −3.2, −0.5] at 3.5 weeks (cycle 1) when compared with baseline ($P = 0.007$; Table 2, Fig. 3). At subsequent visits, there were no significant differences in mean LVEF from baseline (Table 2). Patient and treatment characteristics including hypertension, systolic blood pressure, pulse pressure, and sunitinib starting dose or schedule were not associated with early LVEF changes (Supplementary Table S2). Similarly, early changes in dyspnea severity or the MDASI-HF score were not associated with early LVEF declines (Supplementary Table S2). At baseline, the overall predicted risk of developing LV dysfunction by 33 weeks (cycle 6) following the initiation of sunitinib was 9.7% (95% CI, 3%–17%). The majority of these events occurred by 3.5 weeks of the first treatment cycle, with a substantial decrease in risk over time (Fig. 2C). The estimated risk of LV dysfunction diminished to 5% (95% CI, 0%–11%) and 2% (95% CI, 0%–5%) in patients who had not experienced LV dysfunction by the completion of cycles 1 and 3, respectively.

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Table 1. Baseline patient characteristics ($N = 90$)

Variable	*N* (%)
Age (years)	
Median (IQR)	63 (55–68)
Male sex	59 (66)
Tumor histology	
Clear cell	74 (82)
Papillary	7 (8)
Chromophobe	2 (2)
Other	7 (8)
Site of metastases	
Lung	28 (31)
Liver	7 (8)
Bone	10 (11)
Brain	1 (1)
Other	14 (16)
Unknown	30 (33)
Prior nephrectomy	70 (78)
Prior systemic RCC therapy	
None	78 (87)
IL2	7 (8)
Other targeted agent	5 (6)
Sunitinib starting dose	
50 mg	55 (61)
37.5 mg	4 (4)
25 mg	6 (7)
Other (escalating dose)	25 (28)
Baseline LVEF (%)	
Median (IQR)	49.8 (44.6–54.1)
Baseline cardiac troponin I (pg/mL)	
Median (IQR)	1.7 (1.0–3.6)
Baseline BNP (pg/mL)	
Median (IQR)	32.8 (16.7–65.4)
Baseline SBP (mmHg)	
Median (IQR)	135 (123–147)
Baseline pulse pressure (mmHg)	
Median (IQR)	58 (47–70)
Baseline dyspnea severity[a]	0 (0–2)
Baseline MDASI-HF Score[a]	0.6 (0.2–1.5)
Cardiovascular co-morbidities/risk factors	
Hypertension	49 (54)
Coronary disease	8 (9)
Heart failure	4 (4)
BMI (median, IQR)	27.0 (23.7–32.9)
Hyperlipidemia	47 (52)
Diabetes mellitus	22 (24)
Tobacco use	51 (57)
Cardiac medication use	
Aspirin	23 (26)
ACEi or ARB	24 (27)
Beta blocker	20 (22)
Calcium channel blocker	19 (21)
Statin	28 (31)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SBP, systolic blood pressure; Statin, HMG CoA reductase inhibitor.

[a]Symptoms assessed by the MDASI-HF and scored on a scale of 0–10. Heart Failure Symptom Score is derived from the average response for 8 heart failure symptoms, including severity of ankle edema, abdominal bloating, sudden weight gain, lack of energy, orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough, and palpitations.

Changes in cardiac biomarkers over time

There were no significant changes in either hsTnI or BNP over time across the study cohort (Table 2). However, at baseline, seven participants (7.8%) had an abnormal hsTnI (>21.5 pg/mL), and 15 participants (16.7%) had an abnormal BNP (>100 pg/mL). Only one participant had baseline elevations in both biomarkers. A total of 17 participants (18.9%) developed subsequent cardiac biomarker increases exceeding abnormal thresholds. Six participants (6.7%) developed an increase in hsTnI exceeding the 99th percentile (>21.5 pg/mL) following the initiation of sunitinib therapy. hsTnI elevations occurred in the setting of recent intra-abdominal surgery ($N = 1$) and a recent hospitalization for dehydration and electrolyte derangements ($N = 1$). All hsTnI elevations occurred by week 15 (cycle 3), with the exception of two participants who developed hsTnI elevation at week 33 (cycle 6). Similarly, 11 additional participants (12.2%) developed increases in BNP to >100 pg/mL ($N = 1$ with incident brain metastases, $N = 1$ with malignant ascites, $N = 1$ with end-stage renal disease requiring hemodialysis, and $N = 1$ with hemorrhagic hepatic metastases). Five of these participants had abnormal BNP values (>100 pg/mL) at baseline. All BNP increases occurred by week 15 (cycle 3), with the exception of one participant who developed an increase at week 33. Although there was no significant association between hsTnI and LVEF (0.1% LVEF decline per 10 unit increase in hsTnI, $P = 0.407$), BNP was modestly associated with LVEF change (0.4% decrease in LVEF for 100 unit increase in BNP, $P = 0.007$).

Characteristics and clinical course of patients who developed LV dysfunction

Of the nine participants who experienced incident LV dysfunction, as defined by an absolute LVEF decline by $\geq$10% to an absolute LVEF value of <50%, eight had a sunitinib starting dose of 50 mg daily, and all participants were initially treated on a 4-week-on/2-week-off dosing schedule (Table 3). The median quantitated LVEF at baseline was 53.1%, with three participants having an LVEF < 50% (47.1% to 49.9%). There was no significant difference in the median baseline LVEF between those with and without the development of subsequent LV dysfunction (53.1% vs. 49.2%, $P = 0.105$). Eight of these nine participants developed LV dysfunction by the 3.5-week study visit (cycle 1), and the remaining one patient developed LV dysfunction by the 15-week visit (cycle 3). The median absolute decline in LVEF among these patients was 12.5% (IQR, 12.0–14.7). The majority of participants had nonspecific symptoms, most commonly generalized fatigue. Only two participants with a decline in LVEF also experienced an elevation in hsTnI or BNP. The median changes from baseline for hsTnI and BNP among patients with sunitinib-induced LV dysfunction were 0.6 pg/mL (IQR, −1.9, 6.5) and 4.6 pg/mL (IQR, −2.9, 19.6), respectively (Table 3).

Sunitinib therapy was continued in eight participants and discontinued in one participant. Two participants were not evaluable for improvement in LVEF (both died from mRCC prior to subsequent echocardiography). All evaluable participants had a subsequent improvement in LVEF by 15 to 33 weeks, including the six participants who remained on sunitinib. Four participants had recovery of LVEF to at least within 3% of their respective baseline LVEF. Following the detection of LV dysfunction, four participants initiated new antihypertensive medications, and two had a dose reduction of sunitinib and were changed to a 2-week-on/1-week-off dosing schedule (Table 3). All eight participants who continued sunitinib therapy remained on drug without pause in treatment.

Discussion

Although LV dysfunction is a known cardiovascular toxicity of the VEGF receptor TKI sunitinib, the clinical significance of this

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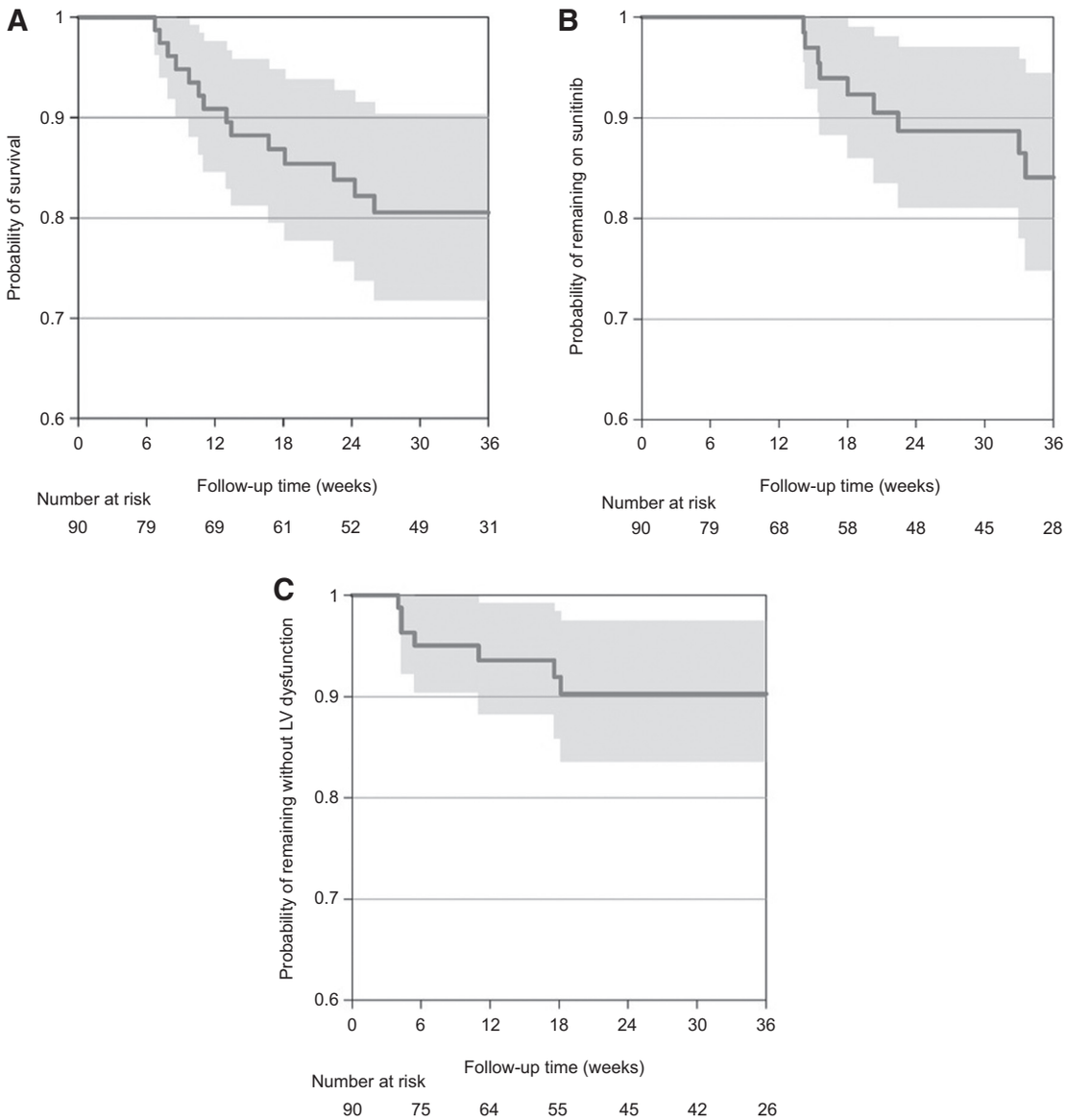

Figure 2.
Kaplan–Meier analyses for (**A**) time to death from mRCC, (**B**) time to sunitinib discontinuation, and (**C**) time to LV dysfunction.

toxicity remains poorly defined. In an effort to improve our understanding of the epidemiology and natural history of LV dysfunction as a result of sunitinib exposure, our prospective study comprehensively evaluated changes in LVEF, derived by quantitative echocardiography, in a "real-world" mRCC cohort. Furthermore, we evaluated circulating cardiac biomarkers as additional surrogate measures of subclinical myocardial injury and stress. Our study revealed several key findings. First, on the population level, patients with mRCC receiving sunitinib demonstrate very modest declines in LVEF and minimal change in plasma cardiac biomarkers. Second, 9.7% of patients do experience a more substantial decline in LV function; however, these patients largely demonstrate recovery of LVEF to near baseline values despite the continuation of sunitinib therapy, but in the

Table 2. Change in LVEF and cardiac biomarkers from baseline

Study timepoint		Change in LVEF (%)[a]	*P* value	Change in hsTnI (pg/mL)[a]	*P* value	Change in BNP (pg/mL)[a]	*P* value
Visit 2	3.5 weeks (±1 week)	−1.9 (−3.2, −0.5)	0.007	−8.1 (−18.3, 2.1)	0.123	21.2 (−23.8, 66.2)	0.361
Visit 3	15 weeks (±2 weeks)	−0.3 (−1.8, 1.2)	0.714	−3.7 (−14.6, 7.2)	0.510	−8.4 (−57.3, 40.4)	0.737
Visit 4	33 weeks (±2 weeks)	0.1 (−1.6, 1.8)	0.933	−6.3 (−18.3, 5.7)	0.308	6.9 (−48.0, 61.7)	0.807

[a]Mean absolute change from baseline, with 95% CI; Analyses performed with linear mixed-effects model with random intercept.

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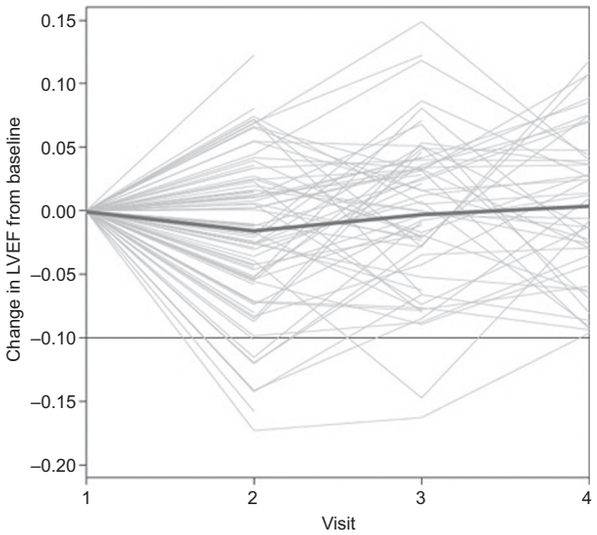

Figure 3.

Change in LVEF from baseline with sunitinib therapy. Trajectory of LVEF plotted for each individual patient. Dark gray line indicates a summary spline curve of mean change in LVEF. Threshold at −0.10 denotes the development of LV dysfunction, as defined by an absolute LVEF decline by ≥10% to a value of <50%.

setting of careful cardiovascular management or sunitinib dose reduction. Third, LV dysfunction occurs early in the treatment course—often within the first treatment cycle—and the subsequent risk of significant subclinical LV dysfunction following three cycles of therapy is low. Fourth, a similar proportion of patients also develop early abnormalities in hsTnI and BNP, which may be more sensitive markers of cardiac injury and stress. We believe these findings have important implications for the cardiovascular and oncologic management of patients on sunitinib therapy, particularly with regard to the timing of cardiovascular assessment and the continuation of therapy.

To our knowledge, this is the first prospective evaluation of sunitinib-induced cardiotoxicity using precise assessment of cardiac function obtained at standardized intervals and quantified in an echocardiography core laboratory. Prior reports of sunitinib-related cardiovascular toxicity have mostly been retrospective in nature, with various composite endpoint definitions, cardiac monitoring procedures, and study populations (9, 17, 19, 20). Overall, retrospective analyses suggest that LVEF declines occur in 18.9% of patients, whereas a larger percentage (33.8%) develops an elevation in cardiac enzymes, symptomatic arrhythmia, or new LV dysfunction (8, 20). However, quantitative echocardiography was not performed in these reports. Many studies also demonstrate some degree of LVEF recovery following sunitinib-induced LV dysfunction (26, 28). Our study definitively validates these findings through its prospective design, standardized data collection, and inclusion of a population that is generalizable to every day practice.

As such, these findings provide important evidence to guide screening and toxicity management with sunitinib in routine clinical practice. Although cardiovascular risk on VEGF receptor TKIs is widely recognized, current consensus statements do not provide guidance for the monitoring of cardiac function (6). As a result, institutional algorithms for the cardiac monitoring of patients treated with VEGF receptor TKIs have been developed and recommend varying strategies, including monthly or every 3-month LVEF assessment (19, 20). In contrast, our data suggest that although cardiovascular toxicity may occur early during therapy (9.7% with LVEF declines of ≥10% to a value of <50%), routine cardiac monitoring in asymptomatic individuals is unlikely to be of widespread clinical benefit, specifically beyond cycle 3 of therapy when the observed rates of cardiac dysfunction were very low (approximately 2% by 33 weeks).

Furthermore, the standard management of mRCC is to exploit the addiction of mRCC to VEGF signaling by utilizing serial VEGF-targeted agents despite disease progression on an initial VEGF receptor inhibitor (3, 29). Thus, early cessation of therapy is not favorable, and novel multitargeted VEGFR inhibitors are achieving unprecedented survival benefit in pretreated patients with mRCC (30). In our study, the majority of patients who experienced a significant decline in LVEF were able to recover LV function to within 3 percentage points of their baseline with careful cardiovascular management. Of note, many patients had initiation of antihypertensive medications and/or dose reduction of sunitinib. However, recovery of cardiac function occurred primarily in the setting of sunitinib continuation/dose reduction and without treatment delay. Although there were no specific clinical risk factors that could be clearly identified, our findings suggest that LVEF declines are largely reversible, and the discontinuation of sunitinib therapy in the setting of incident asymptomatic LV dysfunction is not universally mandated. Our findings suggest that therapy may be continued in these patients with careful cardiovascular and oncologic management in an effort to derive maximum benefit from VEGF-directed therapies with minimal "cost" to treatment intensity. Therefore, the modest and reversible nature of LV dysfunction in our study may provide reassurance regarding cardiotoxicity in this setting, as has been similarly demonstrated in a recent cardiac monitoring study of patients with RCC treated adjuvantly with VEGF receptor TKIs (26).

Elevations in plasma cardiac biomarkers have been prospectively identified as indicators of cardiac toxicity occurring in the absence of overt LV systolic dysfunction (31–33). In retrospective studies of patients with mRCC, cardiac biomarker alterations have similarly been reported following sunitinib initiation, with resulting algorithms recommending routine serial BNP monitoring (19). Although there were no significant mean changes in measures of hsTnI and BNP from baseline following the initiation of sunitinib in our study cohort, a total of 18.9% of patients developed marked increases in hsTnI or BNP. Of note, most of these patients did not have a corresponding detectable substantial decline in LVEF. Therefore, although these biomarker elevations may be indicative of early subclinical cardiac toxicity, the clinical utility of plasma cardiac biomarkers in an advanced oncologic population with multiple clinical confounders is unclear. Indeed, a nontrivial number of patients had baseline biomarker abnormalities, potentially reflecting the sequelae of the oncologic disease burden, common medical comorbidities in this population such as renal disease, and possibly even an increased risk of oncologic mortality (34). Thus, our findings indicate a lack of clear clinical utility for hsTnI or BNP in this setting and suggest the need to understand whether the test characteristics may differ according to the severity of oncologic disease.

In our study, no baseline patient or treatment factors, including sunitinib dose or schedule, were associated with an early LVEF

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Table 3. Clinical characteristics of individual patients experiencing LV dysfunction while on sunitinib

Patient	Age (yrs)	Gender	Baseline cardiac medications	Sunitinib starting dose (mg)	Baseline LVEF (%)	Maximum LVEF decline (%)[a]	Maximum change in biomarker (pg/mL)[b]	HF symptoms	New cardiac medications	Sunitinib continued	LVEF recovery	Recovery LVEF (%)	Timing of LVEF recovery	Notes
1	55	M	BB, statin, diuretic	50	49.9	10.1	TnI: −4.1 BNP: −504	Fatigue, dyspnea	None	Yes	N/A	N/A	N/A	Expired from RCC prior to subsequent ECHO
2	43	M	Statin	50	53.4	17.2	TnI: +227.5 BNP: +3.9	Fatigue	BB, CCB	Yes	Yes	43.8	Wk 33	Changed RCC therapy wk 30 secondary to disease progression
3	56	F	None	50	53.1	14.1	Unk	Fatigue, dyspnea, PND	None	Yes	Yes	67.6	Initial recovery Wk 15; Full recovery by Wk 52	SU dose reduction and changed to 2/1 schedule wk 15
4	41	F	None	50	51.7	14.7	TnI: +0.5 BNP: +5.2	Fatigue, ankle swelling	None	Yes	Yes	50.9	Wk 33	SU dose reduction and changed to 2/1 schedule wk 15
5	61	M	ASA, ARB, CCB, Diuretic	50	47.1	12.0	TnI: +3.8 BNP: +3.8	Fatigue	Clonidine BB	Yes	Yes	57.9	Wk 33	
6	66	M	CCB	50	55.0	12.0	TnI: +0.7 BNP: +23.6	Fatigue, ankle swelling	ARB, diuretic BB	No	Yes	52.0	Wk 33	Changed RCC therapy wk 12 secondary to disease progression
7	46	M	None	37.5	53.5	11.5	TnI: −22.4 BNP: +15.6	Fatigue, dyspnea	ACEi	Yes	Yes	52.6	Wk 15	
8	45	M	ASA	50	49.7	12.5	TnI: +0.3 BNP: −9.5	Fatigue	None	Yes	Yes	46.2	Wk 33	Changed to 2/1 schedule wk 15
9	56	M	BB, CCB, other	50	62.1	15.8	TnI: +9.2 BNP: +1726	None	None	Yes	N/A	N/A	N/A	Expired from RCC prior to subsequent ECHO

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, aspirin; BB, beta-blocker; CCB, calcium channel blocker; ECHO, echocardiography; HF, heart failure; N/A, not applicable; Statin, HMG CoA reductase inhibitor; SU, sunitinib; TnI, high-sensitivity cardiac troponin I; Unk, unknown; Wk, week.

[a]For all patients with the exception of patient 4, LV dysfunction was detected at week 3.5. For patient 4, this was detected at 15 weeks.

[b]Maximum change in biomarker from baseline visit (i.e., biomarker value at follow-up visit—biomarker value at baseline visit).

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decline. Interestingly, although hypertension is a risk factor for heart failure and cardiomyopathy and a widely recognized toxicity of sunitinib therapy, neither baseline systolic blood pressure nor pulse pressure was associated with change in LVEF. It is possible that measures such as blood pressure may not adequately quantify the changes in vascular function that occur with this therapy. Ongoing clinical studies, including detailed phenotyping with arterial tonometry, will seek to clarify the relationship between early changes in systemic vascular load with sunitinib, LV dysfunction, and cardiac recovery. In addition, our sample size may have limited our ability to detect a significant association between patient or treatment factors and early LVEF change.

Additional limitations of this study are noted. In a patient population with an advanced malignancy, disease-related death serves as a competing risk to treatment-related cardiovascular toxicity and may therefore bias the reported risk estimates. In addition, in our study, 23% of participants prematurely withdrew from study follow-up, primarily in the setting of oncologic disease progression. However, the results of the reported conditional survival analyses indicate that if a patient continues on sunitinib therapy without significant LV dysfunction through cycle 3, then the subsequent risk of LV dysfunction is low at 33 weeks. Furthermore, as the majority of active patients remained on sunitinib therapy at cycle 6, or 33 weeks of follow-up, it is unlikely that early cessation of sunitinib therapy significantly affected the reported conditional survival. Finally, our sample size precluded us from determining the relationship between sunitinib-induced LV dysfunction and oncologic outcomes.

When compared with prior reports of sunitinib-induced cardiovascular toxicities, the strengths of this current study include its prospective nature, the detailed assessments performed at predefined intervals designed to coincide with the sunitinib cycle length and drug exposure, and detailed cardiovascular phenotyping with central review of echocardiograms in a core laboratory and cardiovascular biomarker data. In addition, the enrollment of a nonclinical trial patient population with medical comorbidities common to the mRCC population allows for external validity and generalizability of these findings to routine clinical practice.

In conclusion, we found that although the majority of mRCC patients experience modest declines in LVEF and cardiac biomarker changes with sunitinib, 9.7% of patients experience a substantial LVEF change and 18.9% develop cardiac biomarker elevations. LV dysfunction, as defined by LVEF declines, occurs early in the treatment course and is not directly reflected by cardiac symptoms or changes in hsTnI or BNP. Taken together with recently reported cardiac toxicity findings from the adjuvant use of sunitinib, these results indicate that LVEF declines are largely reversible in the setting of sunitinib continuation with careful cardiovascular management or sunitinib dose reduction. While individual clinical discretion remains prudent, routine LVEF or cardiac biomarker monitoring in asymptomatic individuals with a low index of suspicion of cardiotoxicity may be of limited utility, especially beyond three cycles of therapy.

Disclosure of Potential Conflicts of Interest

S. Keefe is currently an employee of Merck. N. Agarwal is a consultant/advisory board member for Eisai, Exelixis, Novartis and Pfizer, and reports receiving commercial research grants from EMD Serono, Novartis and Pfizer. D. Lenihan is a consultant/advisory board member for Amgen, Bristol-Myers Squibb, Prothena, and Roche. B. Ky reports receiving commercial research grants from Pfizer, Roche, and Singulex. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

Sponsors were not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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