

Effects of Adjuvant Sorafenib and Sunitinib on Cardiac Function in Renal Cell Carcinoma Patients without Overt Metastases: Results from ASSURE, ECOG 2805

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Abstract

Purpose: Sunitinib and sorafenib are used widely in the treatment of renal cell carcinoma (RCC). These agents are associated with a significant incidence of cardiovascular (CV) dysfunction and left ventricular ejection fraction (LVEF) declines, observed largely in the metastatic setting. However, in the adjuvant population, the CV effects of these agents remain unknown. We prospectively defined the incidence of cardiotoxicity among resected, high-risk RCC patients treated with these agents.

Experimental Design: Sunitinib, sorafenib, or placebo was administered for up to 12 months in patients with high-risk, resected RCC. LVEF was measured by multigated acquisition (MUGA) scans at standard intervals. Additional CV adverse events were reported according to NCI Common Terminology Criteria for Adverse Events (CTCAE).

Results: Among 1,943 patients randomized, 1,599 had at least 1 post-baseline MUGA. Within 6 months, 21 patients (1.3%) experienced a cardiac event, defined as an LVEF decline from baseline that was >15% and below the institutional lower limit of normal. Nine of 513 patients (1.8%) were on sunitinib, 7 of 508 (1.4%) on sorafenib, and 5 of 578 (0.9%) on placebo ($P = 0.28$ and 0.56 comparing sunitinib and sorafenib to placebo, respectively). With dose interruption or adjustment, 16 of the 21 recovered their LVEF to >50%. The incidence of symptomatic heart failure, arrhythmia, or myocardial ischemia did not differ among groups.

Conclusions: In the adjuvant setting, we prospectively define low incidence of cardiotoxicity with sunitinib and sorafenib. These findings may be related to close CV monitoring, or potentially to fewer CV comorbidities in our nonmetastatic population. *Clin Cancer Res*; 21(18); 4048–54. ©2015 AACR.

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Portions of these results were presented at the ASCO meeting in 2012 (abstract 4500).

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Introduction

Vascular endothelial growth factor receptor (VEGFR) inhibitors improve overall survival and/or progression free survival in metastatic renal cell and other carcinomas (1–7). However, a major concern with the use of the VEGFR tyrosine kinase inhibitors (VEGFR-TKIs) is the unintended adverse cardiovascular (CV) toxicities (8). Sunitinib and sorafenib have each been associated with hypertension, left ventricular systolic and diastolic dysfunction, heart failure (HF), and myocardial ischemia (9–13). A recent meta-analysis suggests an incidence of symptomatic HF of 4.1% with sunitinib in the metastatic setting (12). The incidence of asymptomatic LVEF decline may be even greater, resulting in a growing population of patients with HF and stage B disease (14).

These agents inhibit a number of kinases, and have important "off-target" effects. Sunitinib inhibits VEGFR 1,2,3, platelet-derived growth factor (PDGF), stem cell factor receptor (c-kit), receptor-type tyrosine-protein kinase 3 (FLT-3), colony-stimulating factor-1 and (Flt-1), and sorafenib, also inhibits VEGFR 2,3, and RAF kinases C-raf and B-raf (15, 16). Many of these pathways play fundamental roles in the maintenance of CV function, and response to CV stress (9, 10). As such, there have been clear associations with LVEF decline and subsequent stage B HF. However, all previous reports of cardiotoxicity with VEGFR-TKIs

Translational Relevance

Antiangiogenic tyrosine kinase inhibitors have a significant risk of cardiotoxicity in patients with metastatic disease. In a phase III adjuvant placebo-controlled, double-blind study of adjuvant sorafenib versus sunitinib in high-risk patients with resected renal cell carcinoma, we performed detailed, prospective cardiovascular monitoring with serial assessment of left ventricular ejection fraction (LVEF), with dose interruptions and adjustments when LVEF declines were detected. A detailed blood pressure management algorithm was also incorporated for all patients. Adjuvant sunitinib or sorafenib was associated with a low incidence of cardiotoxicity in this population, and LVEF declines were largely reversible with dose interruptions or modification. Treatment duration was associated with cardiac events, suggesting an important need for continued monitoring while on therapy. Overall, low toxicity rates may be achievable with careful cardiovascular monitoring in the adjuvant setting, with potential implications for patients with other solid tumor malignancies treated with antiangiogenic tyrosine kinase inhibitors.

have been in the setting of metastatic disease, limiting differentiation of treatment from disease related events, and the residual effects of previous anticancer therapy. There is a paucity of data in the adjuvant setting.

ECOG 2805 is a randomized, double-blind phase III trial of 1 year of adjuvant sunitinib, sorafenib, or placebo in previously untreated patients with completely resected RCC at high risk for recurrence (17). Within E2805, we implemented a prospective cardiac monitoring protocol to determine if patients treated with sorafenib or sunitinib in the adjuvant setting experienced clinically significant decreases in LVEF. We also broadly captured additional CV adverse events such as arrhythmia and cardiac ischemia were reported according to NCI Common Terminology Criteria for Adverse Events (CTCAE) at each study visit. We report here the results of a detailed analysis from this substudy detailing the incidence, severity, and reversibility of cardiotoxicity.

Patients and Methods

The E2805 trial (17), led by ECOG (now ECOG-ACRIN) with participation from the Southwest Oncology Group (SWOG), Cancer and Leukemia Group B (now the Alliance), and the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG), accrued 1,943 patients between April 2006 and September 2010. All patients have completed therapy with the full assessment of the prospective cardiac safety substudy. The study was embedded within the clinical trial E2805. Consent for the cardiac substudy was embedded within the phase III trial consent and was approved by Institutional Review Boards before initiation and was conducted in accordance with the Declaration of

Helsinki. All subjects provided informed consent before participation.

Eligibility

Eligible patients had histologically proven, completely resected clear or nonclear cell RCC at high risk for recurrence (clinicaltrials.gov NCT00326898). Patients were treatment-naïve for kidney cancer, had ECOG performance status 0 or 1, and normal organ function. Eligible patients had a normal LVEF of at least 50% by MUGA scan, no cardiac dysfunction or cardiac event [myocardial infarction (MI), severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, or pulmonary embolism] in the 6 months prior to study drug administration, no significant ventricular or atrial arrhythmias, a QTC interval of less than 500 ms, and blood pressure of $\leq 130/90$ mm Hg. We designed the trial to include a very 6-month criteria for major cardiac events, in comparison to prior metastatic renal cell cancer trials, which used a 12-month time period (18) but were not published at the time of the design of this study.

Treatment and disease evaluation

Patients were randomly assigned to receive nine 6-week cycles of either sunitinib 50 mg daily for 28 of 42 days per cycle, sorafenib 400 mg twice daily, or placebo. In 2009, to address toxicity issues, the starting doses were amended to 37.5 mg (sunitinib/placebo) or 400 mg once daily (sorafenib/placebo) for the first 1 to 2 cycles of therapy. Patients experiencing no >grade 1 or tolerable grade 2 side effects were escalated to full doses for subsequent cycles. Dose reductions occurred for grade 3 to grade 4 toxicities (NCI-CTCAE version 3.0). Patients were assessed every 6 weeks for toxicity, and imaged at regular intervals until disease recurrence or through 10 years.

Cardiac assessments

All patients had LVEF measured by MUGA at baseline, 3, 6, 12 months, or at the end of treatment; if cardiac symptoms developed; and 3 months after the last abnormal assessment. MUGA results were based on institutional reporting. Dose modifications for decline in LVEF (Table 1) were derived from prior published algorithms for cardiotoxic agents (19). If dosing was held due to a decline in LVEF, the MUGA was repeated in 2 to 4 weeks. Agents were resumed at the same dose level if the LVEF improved to the institutional lower limit of normal (ILN). If the LVEF improved to within 1% to 5% of ILN, the agents were resumed at one dose level reduction. If the LVEF failed to return to these levels, then agents were held an additional 2 weeks and the MUGA was again repeated. After holding agents for at least 4 weeks, agents were resumed if the LVEF had normalized, or the patient came off study.

Cardiac substudy statistical design

The primary objective of the cardiac substudy was to determine if patients treated with sunitinib or sorafenib experienced

Table 1. Dose modification plan

Resulting LVEF	LVEF decline			
	None	<10%	10%-15%	$\geq 16\%$
0% < ILN	Continue	Continue	Continue	Discontinue treatment
1%-5% < ILN		Continue and repeat MUGA	Continue and repeat MUGA	Hold drug/repeat MUGA
$\geq 6\%$ Below ILN		Continue and repeat MUGA	Hold drug/repeat MUGA	Hold drug/repeat MUGA

Table 2. Patient and disease characteristics

	Adequately assessed (<i>n</i> = 1,599) <i>N</i> (%)	Had primary event (<i>n</i> = 21) <i>N</i> (%)	No primary event (<i>n</i> = 1,578) <i>N</i> (%)
Very high RCC recurrence risk	808 (50.6)	14 (66.7)	794 (50.4)
Clear cell	1,341 (84.0)	19 (90.5)	1,322 (83.9)
PS 0	1,260 (78.9)	14 (66.7)	1,246 (79.1)
Male	1,108 (69.4)	12 (76.2)	1,092 (69.3)
Prior CV history ^a	363 (22.7)	8 (38.1)	355 (22.5)
Hypertension developed in wk 1	494 (32.1)	6 (30.0)	488 (32.1)
Age, median (range)	56 (19–84)	61 (37–71)	56 (19–84)
Age >55 years	872 (54.4)	17 (81.0)	855 (54.1)
Weeks from surgery to baseline MUGA, median (range)	7.4 (0–20.1)	7.6 (–0.6–12.1)	7.7 (1.3–12.7)
Treatment duration (months), median (range)	12.7 (0.3–16.2)	12.6 (1.0–14.4)	12.7 (0.3–16.2)
Baseline LVEF, median (range)	61% (46%–91%)	60% (51%–67%)	61% (46%–91%)

^aDistant history of transient ischemic event, MI, or ischemia; history of arrhythmia; or similar event occurring more than 6 months prior to registration.

significant decreases in LVEF within 6 months relative to placebo, defined according to protocol as an LVEF < ILN, with a decrease of >15 absolute percentage points from baseline (per protocol event definition). Delayed LVEF events were defined as an absolute decline in LVEF of >15% occurring after 6 months. Event rates on each treatment arm were calculated with 90% exact binomial confidence intervals (CI). A sample size of 200 patients per arm (600 total patients) was planned in order to distinguish the following rate differences in LVEF decline: 0.5% versus 4%, 1% versus 5%, or 2% versus 6%. However, to comprehensively characterize changes in cardiac function, we collected MUGA scan information for all patients participating in this adjuvant trial.

In addition, an early safety evaluation was to be conducted if ≥ 4 of the first 100 patients experienced clinical HF. Clinically, significant HF was defined using CTCAE version 3.0 adverse event criteria as left ventricular systolic or diastolic dysfunction: severe symptoms with any activity or from drop in LVEF responsive (grade 3) or refractory to therapy (grade 4). Restrictive cardiomyopathy \geq grade 3 was included as part of the definition. Based upon this decision rule, this early analysis had a high probability (74%) of detecting a true clinical heart failure rate of $\geq 5\%$.

Secondary cardiac outcomes also included cardiac ischemia or MI, arrhythmia. Additional objectives of this cardiac substudy were to describe the natural history of the primary cardiac events over the duration of follow-up, the association between primary cardiac events and clinical risk factors, and delayed declines in LVEF occurring after 6 months. Hypertension, another secondary outcome, will be reported separately.

Statistical analysis

Descriptive statistics were used to characterize patients at baseline. In addition to the 90% exact binomial CIs used to describe event rates, cumulative incidence curves were used to portray the rate at which events occurred over time.

Because there is no single consensus definition for cardiac dysfunction in the setting of VEGFR-TKI therapy, sensitivity analyses were conducted using these other published definitions:

- LVEF decline $\geq 15\%$ to below ILN occurring at any time (per protocol at any time).
- LVEF decline as above, or any grade 2 or higher cardiac toxicity reported as an adverse event regardless of LVEF measurement. CTCAE Version 3 events classified as "Cardiac, General" or "Cardiac, Arrhythmia" other than hypertension, valvular heart

disease, and Cor pulmonale were included (per protocol, including other).

- Absolute reduction in LVEF of $\geq 10\%$ from baseline to <50% \pm symptoms (19–21).
- Absolute reduction of LVEF of $\geq 5\%$ to <55% with symptoms of HF or an asymptomatic reduction of LVEF of $\geq 10\%$ to <55% from baseline [Cardiac Review and Evaluation Committee (CREC); ref. 22].
- Absolute reduction of LVEF $\geq 10\%$ (23).

The Fisher exact test was used to compare event rates on each experimental arm to the control arm, with a two-sided *P* value of 0.025 considered significant (to control the overall type I error for two comparisons at 0.05). Analyses were performed with an intent-to-treat comparison, including each patient on the arm to which they were randomized, and regardless of the time on treatment. We also examined the extent to which the point estimate of the percent of patients with events on each experimental arm fell outside the 90% CI on the control arm. A sensitivity analysis examined events per person-year of follow-up; CIs and comparisons were done using exact Poisson methods.

Multivariable logistic regression models were used to identify factors associated with development of cardiac dysfunction. Differences between patients included and excluded from the analysis were examined using two-sided *t* tests for continuous variables and the Fisher exact test for categorical factors. Analyses were done using SAS version 9.2, Stata version 12.1, and R.

Results

Patient characteristics of the entire analysis population

As shown in the CONSORT diagram (in supplementary material), 1,603 patients with at least 1 follow-up MUGA scan formed the primary analysis population. Of these, 1,315 were considered adequately assessed, as defined above. Patient characteristics are detailed in Table 2. At baseline, one patient was ineligible due to uncontrolled hypertension and three due to persistent atrial fibrillation. Overall, the baseline prevalence of CV risk factors was low.

Patients excluded because of the absence of follow-up scans were slightly older (median age, 57 vs. 56; *P* = 0.04) and more likely to be female (42% vs. 31%, *P* < 0.001). Excluded patients did not differ with respect to baseline performance status (*P* = 0.61) or baseline LVEF (*P* = 0.35). Although exact reasons for not

Table 3. Cardiac events by treatment arm including per protocol and alternative definitions

	Treatment arm						P values from pairwise comparisons	
	Sunitinib (n = 513)		Sorafenib (n = 510)		Placebo (n = 580)		Sunitinib vs. placebo	Sorafenib vs. placebo
	N (%)	90% CI	N (%)	90% CI	N (%)	90% CI		
Per protocol	9 (1.7)	0.9-3.0	7 (1.3)	0.6-2.6	5 (8)	0.3-1.8	0.28	0.56
Per protocol at any time	14 (2.7)	1.7-4.2	10 (1.9)	1.1-3.3	8 (1.3)	0.7-2.5	0.13	0.48
Per protocol, including other	30 (5.8)	4.2-7.9	26 (5.0)	3.6-7.0	28 (4.8)	3.5-6.6	0.50	0.89
CREC criteria	59 (11.5)	9.3-14.1	56 (10.9)	8.8-13.5	48 (8.2)	6.5-10.4	0.08	0.15
Absolute reduction in LVEF of $\geq 10\%$ from baseline to $< 50\%$	27 (5.2)	3.7-7.2	24 (4.7)	3.3-6.6	17 (2.9)	1.9-4.4	0.06	0.15
Absolute reduction in LVEF $\geq 10\%$	84 (16.3)	13.7-19.3	80 (15.6)	13.1-18.6	87 (15.0)	12.6-17.7	0.56	0.80
Any criteria	99 (19.2)	16.5-22.4	92 (18.0)	15.3-21.1	105 (18.1)	15.5-20.9	0.64	1.00

having a follow-up scan were not known, these patients either withdrew before treatment ($n = 49$) or had short treatment duration (median 1.2 months). About half of these patients discontinued because of patient-elected withdrawal.

Per-protocol cardiac safety analyses

The protocol-specified substudy analysis was conducted in August 2009, when 200 patients per arm completed at least one follow-up MUGA after 6 months or an event within 6 months. Fifteen of the 672 patients in this analysis population experienced primary LVEF events, and the minor observed differences in rates among treatment groups were not statistically significant. Furthermore, the safety analysis of clinically significant heart failure among the first 100 patients was not triggered as only two patients experienced LVEF declines and one patient experienced grade 3 restrictive cardiomyopathy.

Primary cardiac event rate as defined by decline in LVEF

As of August 2013, over a maximum follow-up time of 54 months, 21 of the 1,603 patients had experienced a primary cardiac event, defined as LVEF below the ILN, where the decrease was $> 15\%$ absolute percentage points from baseline within 6 months (Table 3). Of these, 9 of 513 (1.7%) patients were on sunitinib (386.4 person-years), 7 of 510 (1.3%) patients were on sorafenib (402.3 person-years), and five of 580 (0.8%) patients were on placebo (519.9 person-years). These rates were not significantly different (Fisher exact $P = 0.28$ and 0.56 comparing sunitinib and sorafenib to placebo, respectively). As shown in Supplementary Table S1, a sensitivity analysis comparing events per person-year of follow-up also did not detect differences based on the primary endpoint definition (Poisson exact $P = 0.17$ and 0.46 comparing sunitinib and sorafenib to placebo, respectively).

Cardiac event rates using alternative definitions

Table 3 also details event rates when considering multiple definitions of cardiotoxicity (20–24). Proportions are shown with 90% exact binomial CIs and P values from pairwise comparisons of arms. There was a trend toward higher event rates with sunitinib based on the CREC definition or using an LVEF decline of $\geq 10\%$ to $< 50\%$ ($P = 0.08$ and 0.06 , respectively). This was more pronounced in the analysis based on person-years ($P = 0.01$ and 0.02 , respectively).

When we compared event rates between patients who began treatment at full dose and those who started at the lower dose, there were no statistically significant differences (Supplementary Table S2). We also explored whether patients who discontinued treatment due to adverse events might have had a lower PS or lower baseline LVEF and therefore more susceptible to cardiac

events, or experienced substantial LVEF declines and thus prematurely discontinued therapy. However, there were also no differences in event rates between these two groups (Supplementary Tables S3a and S3b).

Clinical factors associated with an increased risk of any LVEF declines

Next, we sought to define those clinical variables associated with a cardiac event, defined by any of the criteria listed in Table 3: treatment arm, sex, performance status (0 vs. 1), RCC risk category and histology, method of ascertainment of kidney cancer (incidental vs. symptomatic), baseline systolic and diastolic blood pressure, treatment duration, and baseline LVEF (Table 4). In our multivariable model, male sex, longer treatment duration, and higher LVEF at baseline were associated with increased risk of an event. Although females had higher baseline LVEF than males, there was no statistically significant interaction between gender and LVEF. Baseline blood pressure was not associated with development of cardiac events.

The relationship among baseline LVEF, treatment duration, and likelihood of a cardiac event is complex (Supplementary Tables S4 and S5 and Figs. S1 and S2), and perhaps related to our outcome definition. Supplementary Table S5 shows a similar breakdown for a more constrained event definition, and the interactions are clearly less pronounced.

Reversibility in LVEF declines over time

Figure 1 demonstrates the trajectories of LVEF among 21 patients with primary cardiac events. All but two patients with events reported at least one post-event MUGA LVEF value higher than the nadir. Sixteen of 21 patients had a recovery MUGA scan with an LVEF of $\geq 50\%$. Figure 2 shows the cumulative incidence of LVEF declines $\geq 16\%$.

Symptomatic heart failure

As previously indicated, the rate of symptomatic heart failure, defined as a grade 3 or 4 left ventricular systolic or

Table 4. Multivariable model—factors associated with occurrence of event (any criteria)

Parameter	Levels	OR (95% CI)	Wald P
Arm	Sunitinib vs. placebo	1.23 (0.89-1.69)	0.21
	Sorafenib vs. placebo	1.05 (0.76-1.46)	0.76
Sex	Male vs. female	1.40 (1.04-1.88)	0.03
Treatment duration (months)		1.04 (1.01-1.08)	0.024
Baseline LVEF		1.10 (1.08-1.12)	< 0.0001

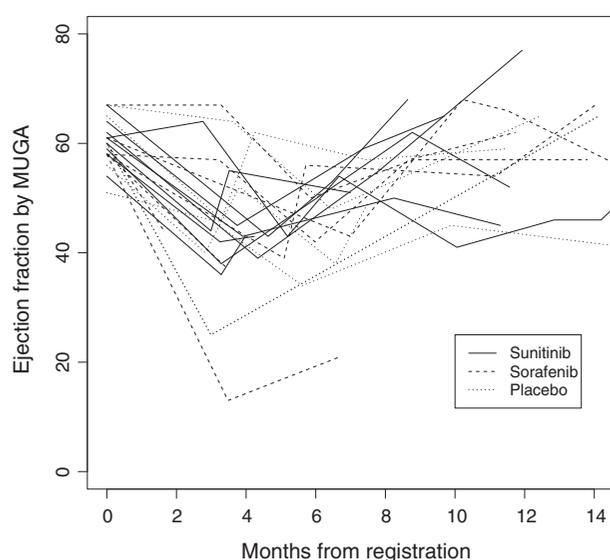


Figure 1. Changes in ejection fraction over time among patients with primary endpoint events, as assessed by MUGA.

diastolic dysfunction, or restrictive cardiomyopathy, was very low. Symptomatic left ventricular systolic dysfunction occurred in five patients in each treatment arm and in two patients on placebo (less than 1% per arm). Six of these patients had protocol-specified events. One report of restrictive cardiomyopathy was documented in a patient treated with sorafenib.

Grade 3 or higher adverse cardiac events

There was an overall low incidence of grade 3 or 4 arrhythmias or cardiac ischemia in the treated groups—five for sunitinib, one for sorafenib, and four for placebo. There were five patients with grade 3 to grade 5 cardiac ischemia, within each of the treatment arms, including placebo.

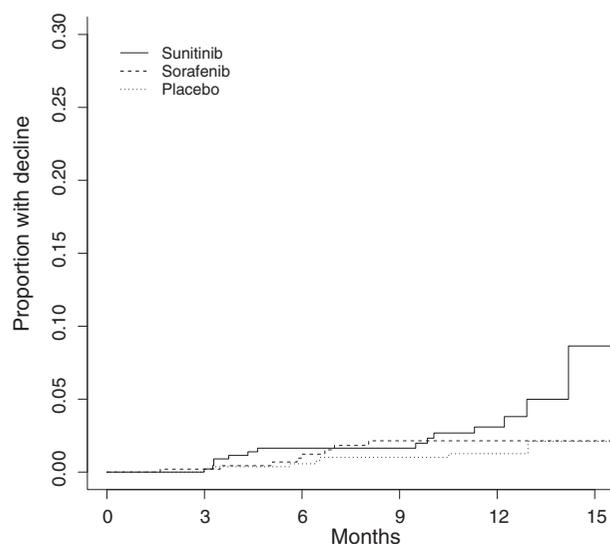


Figure 2. Cumulative incidence of LVEF declines of $\geq 16\%$.

Discussion

Our study is the largest prospective placebo controlled study of the cardiac effects of VEGFR-TKIs and the first in a non-cancer-bearing population. As such, our population presents a unique opportunity to study patients naïve to the effects of prior cardiotoxic regimens and with a relatively low baseline prevalence of CV disease. We found the incidence of significant LVEF decline occurring in the first 6 months of treatment in patients treated with sunitinib or sorafenib to be low. In sensitivity analyses using alternative definitions of cardiac dysfunction, this remained low, with only very modest differences when we considered person-years in our analyses. The number of late declines in LVEF was also not statistically different among the three groups.

It is critical to note that in E2805, patients were carefully screened and those with baseline CV comorbidities were excluded from study participation. As such, these patients may have a lower prevalence of CV disease compared to metastatic populations exposed to these agents, although this comparison is limited (13, 25). Further study patients were monitored for asymptomatic declines in LVEF and CV risk factors were also aggressively managed. Patients underwent dose interruptions and adjustments when these initial declines in LVEF were detected. Furthermore, an algorithm for blood pressure management, which can exacerbate LV dysfunction, was closely followed for all patients on the study (Supplementary Fig. S2). The impact of these interventions in lowering the rate of symptomatic events is unknown, and impossible to discern without a concurrent control group receiving continued treatment and no CV monitoring. It is certainly possible that the incidence of cardiac dysfunction could have been higher if intervention had not occurred in asymptomatic patients. Therefore, our study provides insight into the potential benefits of close CV monitoring and prompt hypertension treatment in patients with RCC receiving sunitinib or sorafenib and at any stage.

Patients on this trial who experienced primary cardiac events had more advanced RCC prior to resection, tended to be older, and had a slightly higher incidence of CV risk factors. Furthermore, longer treatment duration, male sex, and higher baseline LVEF were associated with the risk of any subsequent cardiac events. The treatment duration effect suggests that longer-term exposure results in a stronger cardiotoxic signal, which has important implications for the need for continued CV monitoring through therapy. We saw no difference in event rate according to starting dose, suggesting that a lead-in lower dose could not reduce the already low incidence of CV toxicity. The relationship between baseline LVEF and cardiac events is admittedly counter-intuitive, but may be because of our outcome definition and in particular the variability of LVEF results within the reference range. Importantly, patients with decline in LVEF generally demonstrated some recovery in LVEF with dose interruption.

Limitations

There are limitations worth noting. The trial eligibility criteria excluded patients possibly more susceptible to effects on LVEF. The potential interaction between incident hypertension and LV dysfunction will be elucidated in a planned future study. Furthermore, cardiotoxicity assessment by LVEF alone is limited in its ability to detect subclinical damage to the myocardium and does not provide insight into alterations in diastolic function. Patients

on sunitinib may have experienced declines in LVEF on therapy, which reverted during the 2 weeks off-therapy. The impact of such reversible declines remains unknown, and the long-term CV effects of transient, possibly repeated declines in LVEF need to be elucidated in longer-term studies, perhaps in other oncologic populations.

Finally, we note that patients who did not stay on therapy long enough to participate in 6-month MUGA scans due to treatment limiting toxicity may comprise a population more at risk for LVEF decline.

Implications for current and future use of these agents

Our study has a number of important implications. First, adjuvant sunitinib or sorafenib was associated with a low incidence of cardiotoxicity in the nonmetastatic, treatment-naïve RCC clinical trial population. With the growing use of these agents and potential for use of these agents adjuvantly in patients with high-risk primary or completely resected metastatic solid cancers, this finding alone is noteworthy. Furthermore, in our experience, LV dysfunction was largely reversible with the institution of dose interruption or modification in a population where cardiac adverse effects were very carefully monitored. However, treatment duration was associated with cardiac events, suggesting an important need for continued monitoring while on therapy. Applying these findings to the use of VEGF-TKIs in all settings imply that low toxicity rates may be achievable with careful CV monitoring.

Disclosure of Potential Conflicts of Interest

B. Ky reports receiving a commercial research grant from Pfizer. L. Wood is a consultant/advisory board member for Pfizer. C.G. Wood reports receiving commercial research grants from Argos, GlaxoSmithKline, and Pfizer. M.B. Atkins is a consultant/advisory board member for Bristol-Myers Squibb, GSF, Novartis, and Pfizer. J.J. Dutcher reports receiving speakers bureau honoraria from Pfizer and is a consultant/advisory board member for Pfizer and Prometheus. R.S. DiPaola reports receiving a commercial research grant from AbbVie. No potential conflicts of interest were disclosed by the other authors.

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Authors' Contributions

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