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ARTICLE

Hypertension as a Biomarker of Efficacy in Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib

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Background Hypertension (HTN) is an on-target effect of the vascular endothelial growth factor pathway inhibitor, sunitinib. We evaluated the association of sunitinib-induced HTN with antitumor efficacy and HTN-associated adverse events in patients with metastatic renal cell carcinoma.

Methods This retrospective analysis included pooled efficacy (n = 544) and safety (n = 4917) data from four studies of patients with metastatic renal cell carcinoma who were treated with sunitinib 50 mg/d administered on a 4-week-on 2-week-off schedule (schedule 4/2). Blood pressure (BP) was measured in the clinic on days 1 and 28 of each 6-week cycle. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan–Meier methods; hazard ratios (HRs) for survival were also estimated by a Cox proportional hazards models using HTN as a time-dependent covariate. Efficacy outcomes were compared between patients with and without HTN (maximum systolic BP [SBP] ≥140 mm Hg or diastolic BP [DBP] ≥90 mm Hg). Adverse events were also compared between patients with and without HTN (mean SBP ≥140 mm Hg or mean DBP ≥90 mm Hg). All *P* values were two-sided.

Results Patients with metastatic renal cell carcinoma and sunitinib-induced HTN defined by maximum SBP had better outcomes than those without treatment-induced HTN (objective response rate: 54.8% vs 8.7%; median PFS: 12.5 months, 95% confidence interval [CI] = 10.9 to 13.7 vs 2.5 months, 95% CI = 2.3 to 3.8 months; and OS: 30.9 months, 95% CI = 27.9 to 33.7 vs 7.2 months, 95% CI = 5.6 to 10.7 months; $P < .001$ for all). Similar results were obtained when comparing patients with vs without sunitinib-induced HTN defined by maximum DBP. In a Cox proportional hazards model using HTN as a time-dependent covariate, PFS (HR of disease progression or death = .603, 95% CI = .451 to .805; $P < .001$) and OS (HR of death = .332, 95% CI = .252 to .436; $P < .001$) were improved in patients with treatment-induced HTN defined by maximum SBP; OS (HR of death = .585, 95% CI = .463 to .740; $P < .001$) was improved in patients with treatment-induced HTN defined by maximum DBP, but PFS was not. Few any-cause cardiovascular, cerebrovascular, ocular, and renal adverse events were observed. Rates of adverse events were similar between patients with and without HTN defined by mean SBP; however, hypertensive patients had somewhat more renal adverse events (5% vs 3%; $P = .013$).

Conclusions In patients with metastatic renal cell carcinoma, sunitinib-associated HTN is associated with improved clinical outcomes without clinically significant increases in HTN-associated adverse events, supporting its viability as an efficacy biomarker.

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Hypertension (HTN) is commonly associated with angiogenesis inhibitors that target the vascular endothelial growth factor (VEGF) pathway and appears to be a generalized effect of this class of agents, including sunitinib, bevacizumab, sorafenib, and axitinib, which are newly developed targeted therapies for metastatic renal cell carcinoma (1–6). Physiologically, HTN develops when VEGF stimulates production of nitric oxide and prostacyclins in vascular endothelial cells (7,8), vasodilatory mechanisms become inhibited, and peripheral vascular resistance increases, leading to increased blood pressure (BP). In addition, there is evidence to suggest that HTN may result from structural or functional vascular rarefaction caused by inhibition of angiogenic growth factors (9). HTN may also result from decreased glomerular filtration rate and increased sodium and water retention by the kidney, similar to pre-eclampsia-associated HTN, which has been linked to placental-derived soluble antiangiogenic factors including VEGF (10).

Sunitinib malate (SUTENT; Pfizer Inc, New York, NY) is an orally administered receptor tyrosine kinase inhibitor that targets

CONTEXT AND CAVEATS

Prior knowledge

Hypertension (HTN) is a well-known side effect in some cancer patients who are treated with the vascular endothelial growth factor pathway inhibitor, sunitinib, but it was not clear whether sunitinib-induced HTN is a biomarker of cancer treatment efficacy.

Study design

A retrospective efficacy analysis measured the association of sunitinib-induced HTN with progression-free survival, overall survival, and hazard ratios for survival using data from two phase II trials (N = 63 and N = 106) and one phase III trial (N = 375) for metastatic renal cell carcinoma. In parallel analyses, HTN was defined by either maximum systolic blood pressure (SBP, ≥140 mm Hg) or maximum diastolic blood pressure (DBP, ≥90 mm Hg). A retrospective safety analysis examined the association of sunitinib-induced HTN with adverse events using data from the same three trials and from an additional expanded access trial (N = 4371). In the safety analysis, HTN was defined by a mean SBP of at least 140 mm Hg.

Contribution

Metastatic renal carcinoma patients with sunitinib-induced HTN defined by maximum SBP (≥140 mm Hg) had longer progression-free survival and overall survival than patients without treatment-induced HTN. Results were similar for patients with sunitinib-induced HTN defined by DBP. Overall survival appeared to be improved in patients with both SBP- and DBP-defined HTN. HTN-associated adverse events were slightly higher in patients with a mean SBP at or above (vs below) 140 mm Hg (overall, 11% vs 9%, for renal events, 5% vs 3%).

Implications

The association of sunitinib-induced HTN with improved survival makes it a potential biomarker for treatment efficacy among patients with metastatic renal cell carcinoma.

Limitations

The results were drawn retrospectively from four clinical trials with variable populations and parameters. Some patients were given antihypertensive drugs, and it is not entirely clear how this affects the data. For HTN to be considered a true biomarker in this setting, a validation set and further prospective trials would be needed.

From the Editors

VEGF receptors and other receptor tyrosine kinases (PDGFR, KIT, FLT-3, CSF-1R, and RET). Sunitinib has been approved worldwide for the treatment of advanced renal cell carcinoma. In a randomized phase III trial that tested first-line therapy for metastatic renal cell carcinoma (11), sunitinib was superior to interferon-α in progression-free survival (PFS; 11 vs 5 months; $P < .001$) and objective response rate (ORR; 47% vs 12%; $P < .001$); in addition, median overall survival (OS) with sunitinib was 26.4 vs 21.9 months with interferon-α. Based on these data, sunitinib is currently a standard initial treatment for patients with advanced renal cell carcinoma. Sunitinib was also associated with a 34% incidence of any-grade HTN (including a 13% incidence of grade 3 HTN), which was reported as an adverse event in this trial (12).

Treatment-induced HTN has been proposed as a potential biomarker of the clinical effect of antiangiogenic agents. For example, in a retrospective analysis across multiple tumor types, we demonstrated an association between the occurrence of diastolic BP (DBP) of at least 90 mm Hg and clinical outcome in patients (most notably those with metastatic renal cell carcinoma) who received the potent and selective VEGF receptor inhibitor axitinib (13). In addition, the onset of HTN has been associated with improved clinical outcome in patients receiving other targeted agents, such as those who received the anti–VEGF monoclonal antibody bevacizumab for the treatment of multiple tumor types that included advanced renal cell carcinoma, non–small cell lung cancer, and pancreatic and colorectal cancers (14–17).

Based on these observations, a retrospective analysis was performed to evaluate whether the development of HTN in sunitinib-treated patients with metastatic renal cell carcinoma was associated with its antitumor efficacy and development of HTN-associated complications in target organs. From this study, we sought to determine whether sunitinib-associated HTN could be a biomarker of efficacy without unacceptable toxicity. To our knowledge, the current report represents the largest retrospective analysis of a VEGF receptor inhibitor in a uniform disease state. Efficacy and safety data were pooled from three clinical trials of single-agent sunitinib, and the safety analysis additionally included data from an expanded access protocol that enrolled more than 4000 patients (18).

Subjects and Methods

Patients

Data from sunitinib-treated patients in four clinical trials were included in this analysis: two second-line phase II trials (N = 63 and N = 106), one first-line phase III trial (N = 375), and an expanded access trial (N = 4371) (18–21). Common eligibility criteria for all patients in these analyses included age 18 years or older with histologically confirmed metastatic renal cell carcinoma, adequate organ function, absence of any clinically significant cardiac events (including myocardial infarction, congestive heart failure, or coronary artery bypass graft) within 6 or 12 months of study entry depending on the protocol, and the absence of cardiac dysrhythmia or severe or unstable angina, either ongoing or within 12 months of study entry. Common eligibility criteria for patients that were in the efficacy analysis also included the presence of measurable disease, absence of known brain metastases, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and normal QTc interval. Uncontrolled HTN was explicitly listed as an exclusion criterion in the two phase II trials included in this analysis.

Design

To investigate the relationship between HTN and antitumor efficacy, this retrospective analysis included pooled data from 544 sunitinib-treated metastatic renal cell carcinoma patients in the three prospective multinational clinical trials (19–21). Ten patients were excluded due to lack of post-baseline BP. Patients were administered sunitinib as either second- or first-line treatment of metastatic renal cell carcinoma as noted above. Sunitinib was administered at a starting dose of 50 mg orally once daily for 4 consecutive weeks followed by 2 weeks off treatment (schedule 4/2) in repeated 6-week cycles until progression of disease, lack of clinical benefit, or unacceptable toxicity. Antihypertensive medications and/or sunitinib dose schedule modifications were used to manage HTN as per each clinical trial protocol and at the discretion of the investigator. Efficacy

was measured as ORR [the proportion of patients who had either a complete or partial response as assessed by investigators according to Response Evaluation Criteria in Solid Tumors (22)], PFS, and OS.

The safety portion of the analysis was augmented to include patients from an expanded access trial of metastatic renal cell carcinoma (18) that provided an additional 4373 patients, bringing the total sample size to 4917 patients. Because they lacked post-baseline BP measurements, 498 patients were excluded. The HTN-associated complications evaluated in this analysis included prespecified cardiovascular, cerebrovascular, ocular, and renal adverse events as described by Chobanian et al. (23). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

HTN was defined by either maximum or mean systolic BP (SBP) of at least 140 mm Hg or DBP of at least 90 mm Hg, as measured in the clinic on days 1 and 28 of each 6-week treatment cycle at any time during the study after the first dose of sunitinib. These thresholds were prospectively chosen before data analysis based on published guidelines (23). Maximum (and not mean) SBP and DBP were used for efficacy analyses because subsequent dose reduction of sunitinib and/or antihypertensive medication could have affected mean BP values. Mean (not maximum) SBP and DBP were used for safety analyses and were calculated based on an average of eight post-baseline measurements over a range of 1–33 cycles.

Statistical Methods

PFS and OS were estimated using the Kaplan–Meier method, and a log-rank test was used to compare results between groups of patients with vs without HTN. A Pearson χ^2 test and Fisher exact test were used to compare ORR and selected HTN-associated complications between both groups, respectively. The influence on PFS and OS of selected baseline prognostic risk factors [including the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria (24) and criteria developed for patients with metastatic renal cell carcinoma receiving VEGF inhibitors (25)] was analyzed with the use of a Cox proportional hazards model with each factor investigated in univariate and then multivariable analyses with a backward stepwise algorithm. Factors in the univariate analysis with a P value of less than .2 were entered into the multivariable model, and additional elimination was applied to identify statistically significant variables (at the $P < .05$ level).

A Cox proportional hazards model that considered onset of HTN as a time-dependent covariate was also used to estimate hazard ratios for PFS and OS. Landmark analyses using the Kaplan–Meier method were conducted to assess whether early HTN was associated with either PFS or OS. In these analyses, HTN was defined by maximum SBP of at least 140 mm Hg or DBP of at least 90 mm Hg experienced by the end of cycle 1 (6 weeks) and cycle 2 (12 weeks). Patients who died or had disease progression or death before each landmark were excluded from the OS and PFS analyses, respectively.

All P values were two-sided, confidence intervals (CI) were set at the 95% level, and no adjustment was made for multiple comparisons; thus, P values less than .05 were considered statistically significant. Pearson correlation tests were used to measure the correlation between sunitinib dosing and maximum BP.

Results

Patients

Most patients in the four trials included in this retrospective analysis were men with a mean age of 56–62 years. Most had an ECOG PS of 0 or 1, had undergone prior nephrectomy, and had metastatic renal cell carcinoma with clear cell histology. Baseline patient characteristics were typical for patients with metastatic renal cell carcinoma (Table 1).

Table 1. Baseline patient characteristics*

Characteristic	Phase II trial 1 (N = 63)	Phase II trial 2 (N = 106)	Phase III trial (N = 375)†	Expanded access trial (N = 4371)‡
Mean age, y (range)	60 (24–87)	56 (32–79)	62 (27–87)	59.0 (19.0–89.0)
Male/female, %	68/32	63/37	71/29	74/26
ECOG PS, n (%)				
0	34 (54)	58 (55)	231 (62)	1823 (42)
1	29 (46)	48 (45)	144 (38)	1872 (43)
2	0	0	0	503 (12)
3	0	0	0	73 (2)
4	0	0	0	6 (<1)
Histology, n (%)				
Clear cell	55 (87)	105 (99)	375 (100)	3758 (86)
Other	8 (13)	1 (1)	0	588 (13)
Prior nephrectomy, n (%)	58 (92)	106 (100)	340 (91)	3873 (89)
Prior cytokine therapy, n (%)	63 (100)	106 (100)	0	2974 (68)
Prior radiation therapy, n (%)	25 (40)	20 (19)	53 (14)	NA
No. of disease sites, n (%)				
0	0	0	0	49 (1)
1	8 (13)	13 (12)	55 (15)	833 (19)
≥2	55 (87)	93 (88)	320 (85)	3489 (80)

* Data are from four clinical trials: phase II trial 1 (19), phase II trial 2 (20), phase III trial (21), expanded access trial (18). ECOG PS = Eastern Cooperative Oncology Group performance status; NA = not available.

† The 375 patients cited in the table are those who were randomized to receive sunitinib in this trial.

‡ The sample of 4371 patients in the expanded access trial, as cited in this table, differs from the total number of patients included in the safety analysis (n = 4373) due to different data cutoff dates; as a result, the safety analysis population included 4917 patients.

BP Assessment and HTN Status

Among those patients who had HTN while on treatment, as defined by post-baseline maximum SBPs of at least 140 mm Hg or maximum DBPs of at least 90 mm Hg, median baseline SBP to DBP ratio was 132 mm Hg over 80 mm Hg. Among those patients who did not have HTN while on treatment by the same criterion, median baseline SBP to DBP ratio was 120 mm Hg over 70 mm Hg. Of the 544 patients included in the efficacy analyses, 442 (81%) had systolic-defined HTN and 363 (67%) had diastolic-defined HTN, each recorded at any time after cycle 1, day 1. Of note, the incidences of HTN as defined in this analysis were more frequent than those in which HTN was reported as an adverse event (12) because of the different measures of absolute SBP over DBP and CTCAE grading used. The onset of treatment-induced HTN was early, with median times to systolic- and diastolic-defined HTN during cycle 1 (range 1–20) and cycle 2 (range 1–19), respectively. We found that 58% of patients had systolic-defined HTN and 48% had diastolic-defined HTN by the end of cycle 1; 80% had systolic-defined HTN and 68% had diastolic-defined HTN by the end of cycle 2. The median (range) post-baseline SBP to DBP ratio in patients with HTN was 160 (140–220) mm Hg over 98 (90–129) mm Hg, whereas the median (range) post-baseline SBP to DBP ratio in patients without HTN was 130 (100–139) mm Hg over 82 (59–89) mm Hg.

Relative sunitinib dose intensity (the ratio of actual sunitinib dose intensity received to intended sunitinib dose intensity) was weakly correlated with maximum SBP (r = .13) and DBP (r = .17). Cumulative sunitinib dose up to the time of maximum BP was also weakly correlated with maximum SBP (r = .33) and DBP (r = .27).

Association of HTN With Antitumor Efficacy of Sunitinib

Median PFS (figure not shown) and OS (Figure 1) were differentiated by HTN status, as defined by a maximum SBP of at least 140 mm Hg or a maximum DBP of at least 90 mm Hg, and development of treatment-induced HTN was associated with better clinical outcomes (Table 2). The ORR was 54.8% in patients with vs

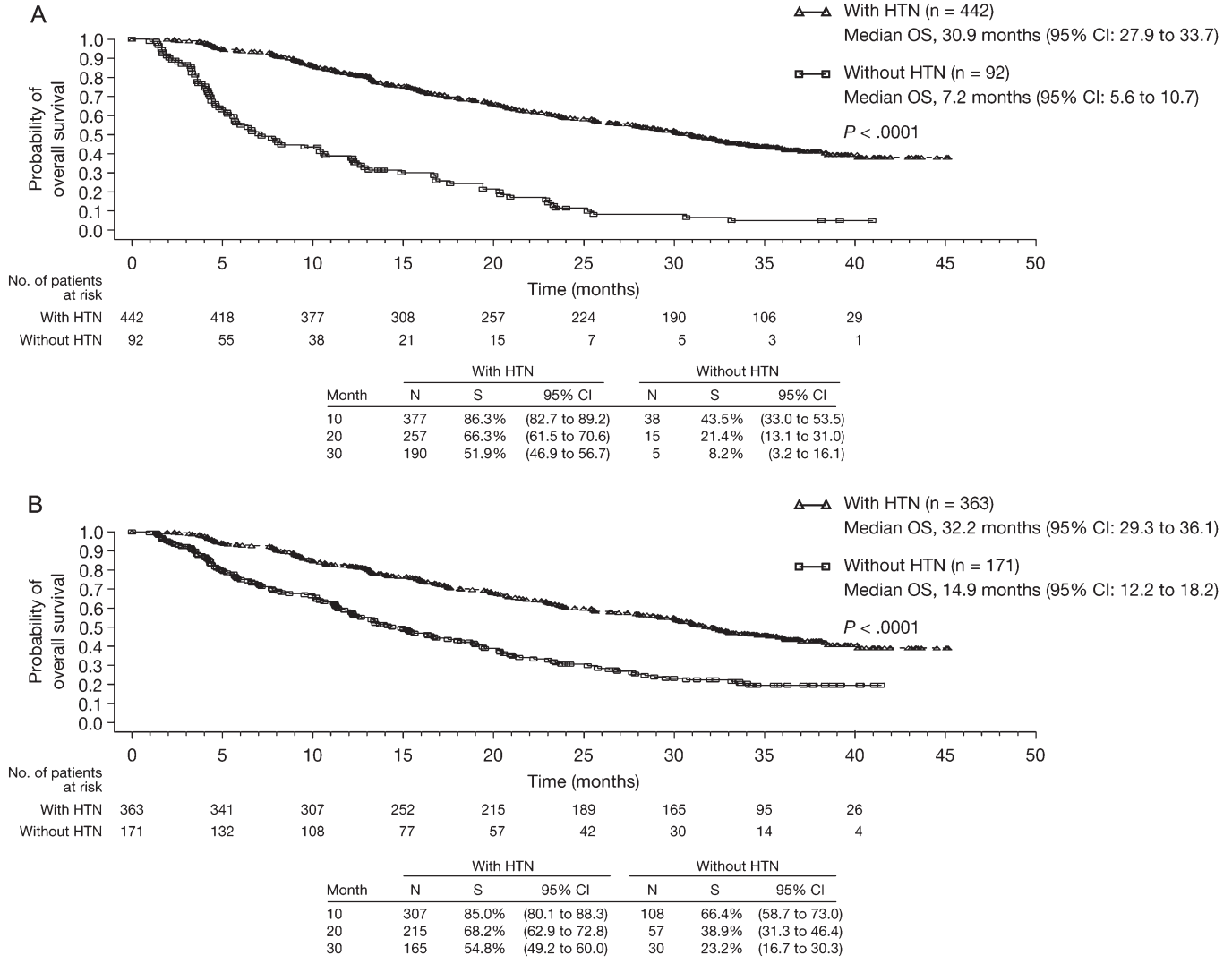


Figure 1. Kaplan–Meier estimates of overall survival (OS) by hypertension (HTN) status (post-cycle 1, day 1). In (**A**) HTN is defined by a maximum systolic blood pressure of at least 140 mm Hg. In (**B**), HTN is defined by a maximum diastolic blood pressure of at least 90 mm Hg. N = number at risk; S = survival percentage, with 95% confidence interval (CI) in parentheses.

Table 2. Objective response and median progression-free and overall survival by hypertension (HTN) status*

Patient HTN status	Total no. of patients	Objective response rate, n (%)†	*P*‡	Progression-free survival (95% CI), mo	*P*‡	Overall survival (95% CI), mo	*P*‡
Maximum SBP ≥ 140 mm Hg	442	242 (54.8)		12.5 (10.9 to 13.7)		30.9 (27.9 to 33.7)	
Maximum SBP <140 mm Hg	92	8 (8.7)	<.001	2.5 (2.3 to 3.8)	<.001	7.2 (5.6 to 10.7)	<.001
Maximum DBP ≥ 90 mm Hg	363	208 (57.3)		13.4 (11.3 to 13.8)		32.2 (29.3 to 36.1)	
Maximum DBP < 90 mm Hg	171	42 (24.6)	<.001	5.3 (4.2 to 7.8)	<.001	14.9 (12.2 to 18.2)	<.001

* Hypertension was defined as maximum SBP of at least 140 mm Hg or a maximum DBP of at least 90 mm Hg. CI = confidence interval; DBP = diastolic blood pressure; SBP = systolic blood pressure.

† Complete response plus partial response as assessed by investigators according to Response Evaluation Criteria in Solid Tumors (22).

‡ *P* values for objective response rate are from a two-sided Pearson χ^2 test, and *P* values for progression-free and overall survival are from a two-sided log-rank test.

8.7% in patients without a maximum SBP of at least 140 mm Hg (*P* < .001). Median PFS was 12.5 months (95% CI = 10.9 to 13.7 months) vs 2.5 months (95% CI = 2.3 to 3.8 months), and median OS was 30.9 months (95% CI = 27.9 to 33.7 months) vs 7.2 months (95% CI = 5.6 to 10.7 months) in the same two groups, respectively. Results were similar when HTN status was defined by a maximum DBP of at least 90 mm Hg (Table 2).

When we looked for an association of median OS with HTN status and defined HTN as a mean (instead of maximum) SBP of at least 140 mm Hg or a mean DBP of at least 90 mm Hg, we observed similar results, although to a lesser extent (data not shown). However, we observed no difference in median PFS when HTN status was defined by mean BP thresholds.

To determine whether or not antihypertensive agents reduced the antitumor efficacy of sunitinib given the observed association of HTN with efficacy, clinical outcomes were compared in patients using these medications at baseline with those who were not using antihypertensive agents. There was no statistically significant difference in ORR between patients who were taking antihypertensive agents at baseline (n = 213) and those who were not (n = 331; *P* = .379). Median PFS in patients taking antihypertensive agents at baseline (n = 213) compared with those who were not (n = 331) was 11.3 months (95% CI = 10.6 to 13.7 months) compared with 10.6 months (95% CI = 8.3 to 11.0 months; *P* = .020), and median OS was 31.8 months (95% CI = 25.5 to 40.1 months) vs 21.4 months (95% CI = 18.2 to 25.0 months; *P* < .001).

To address potential bias from patients who lived longer having longer drug exposure and, therefore, greater opportunity to develop HTN, we used a Cox proportional hazards model with the onset of HTN as a time-dependent covariate. The relative risk of renal cell carcinoma progression and death decreased in patients who developed HTN while on sunitinib with statistical significance in three of the four indices evaluated (Table 3). That is, PFS and OS were both improved (HR = .603, 95% CI = .451 to .805; and HR = .332, 95% CI = .252 to .436, respectively; *P* < .001 for both) in patients with treatment-induced HTN defined by maximum SBP. Overall survival (HR = .585, 95% CI = .463 to .740; *P* < .001), but not PFS, was improved in patients with treatment-induced HTN defined by maximum DBP.

To address potential bias from misclassification of patients who may not have remained on study long enough for HTN to be observed, landmark analyses were conducted that explored the relationship between HTN and clinical outcome. Patients with vs without HTN at the end of cycle 1 (figures not shown), as defined by maximum SBP of at least 140 mm Hg, had a PFS of 13.4 months (95% CI = 11.0 to 14.3 months) vs 10.8 months (95% CI = 9.8 to 13.4 months; *P* = .031) and an OS of 32.2 months (95% CI = 28.1 to "not reached" months) vs 20.3 months (95% CI = 17.0 to 23.2 months; *P* <. 001), respectively. Patients with vs without HTN at the end of cycle 1, as defined by maximum DBP of at least 90 mm Hg, had a PFS of 12.0 months (95% CI = 10.7 to 13.6 months) vs 11.8 months (95% CI = 10.7 to 13.7 months; *P* = .612) and an OS of 30.1 months (95% CI = 23.6 to 32.5 months) vs 23.3 months (95% CI = 20.3 to 27.9 months; *P* = .155), respectively.

Patients with vs without HTN at the end of cycle 2, as defined by a maximum SBP of at least 140 mm Hg, had a PFS (figure not shown) of 13.6 months (95% CI = 12.4 to 16.1 months) vs 10.8 months (95% CI = 8.8 to 13.4 months; *P* = .015) and an OS (Figure 2) of 31.1 months (95% CI = 27.9 to 35.2 months) vs 18.2 months (95% CI = 14.0 to 21.0 months; *P* <. 001). Patients with vs without HTN at the end of cycle 2, as defined by maximum DBP of at least 90 mm Hg, had a PFS (figure not shown) of 13.6

Table 3. Hazard ratios (HRs) for progression-free and overall survival with hypertension (HTN) as a time-dependent covariate in a Cox proportional hazards model*

Patient HTN status	Progression-free survival HR (95% CI)	*P* †	Overall survival HR (95% CI)	*P* †
Maximum SBP ≥ 140 mm Hg	0.603 (0.451 to 0.805)	<.001	0.332 (0.252 to 0.436)	<.001
Maximum DBP ≥ 90 mm Hg	0.992 (0.792 to 1.243)	.947	0.585 (0.463 to 0.740)	<.001

* Hypertension was defined as maximum SBP of at least 140 mm Hg or a maximum DBP of at least 90 mm Hg. CI = confidence interval; DBP = diastolic blood pressure; SBP = systolic blood pressure .

† *P* values are from a two-sided log-rank test.

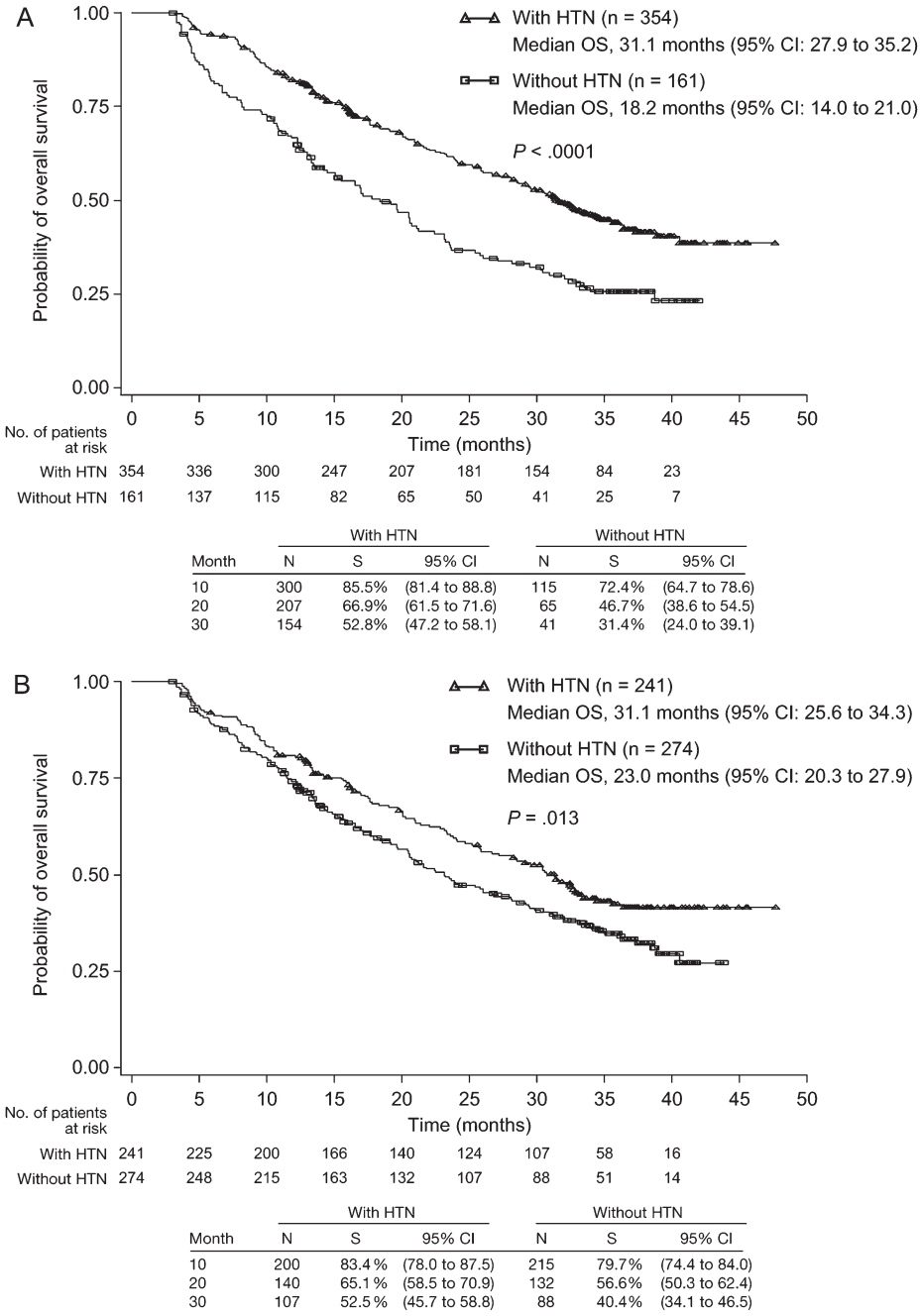


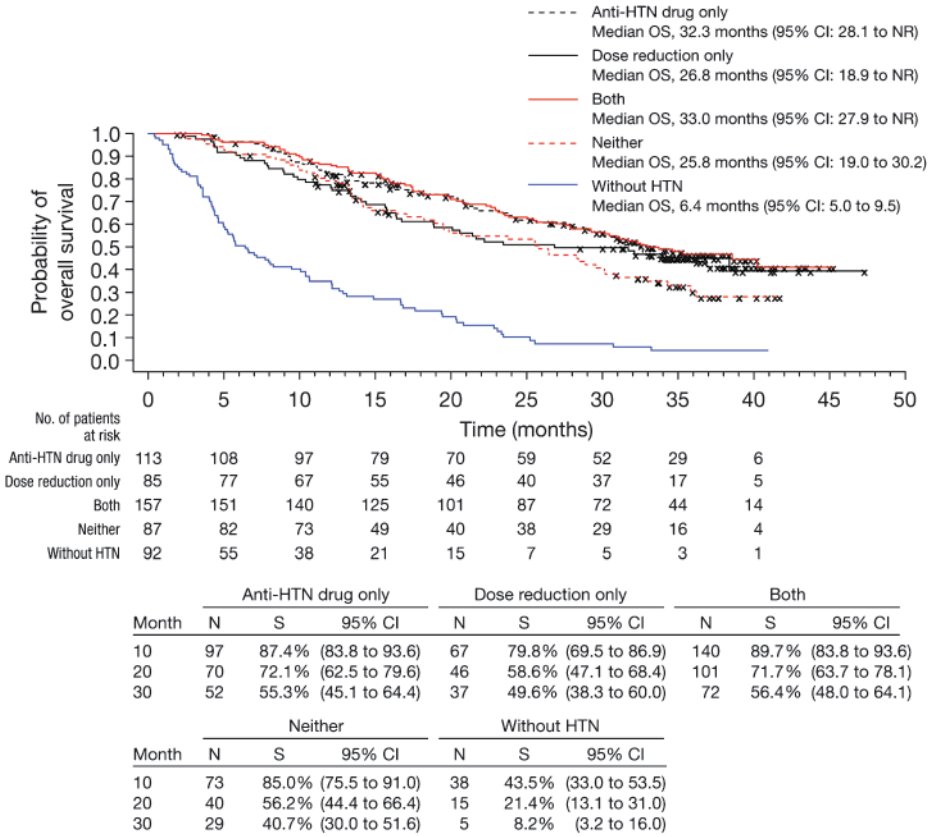
Figure 2. Kaplan–Meier estimates of overall survival (OS) by hypertension (HTN) status experienced by the end of cycle 2 (12 weeks). In (**A**), HTN is defined by a maximum systolic blood pressure of at least 140 mm Hg. In (**B**), HTN is defined by a diastolic blood pressure of at least 90 mm Hg. N = number at risk; S = survival percent, with 95% confidence interval (CI) in parentheses.

months (95% CI = 11.3 to 16.1 months) vs 13.4 months (95% CI = 10.8 to 14.3 months; $P = .760$) and an OS (Figure 2) of 31.1 months (95% CI = 25.6 to 34.3 months) vs 23.0 months (95% CI = 20.3 to 27.9 months; $P = .013$), respectively.

To understand how the management of treatment-induced HTN might affect subsequent clinical outcomes, we undertook an exploratory subset analysis. Patients with HTN were subdivided into four hypertensive patient management groups: 1) addition of antihypertensive agent only, 2) sunitinib dose reduction only, 3) both maneuvers, and 4) neither maneuver. Graphical analysis of PFS (figure not shown) and OS (Figure 3) demonstrated that patients with HTN (as defined by a maximum SBP of at least 140 mm Hg) continued to survive longer than patients without HTN, independent of use of antihypertensive agents, HTN-induced dose reductions, or both.

Progression-Free and Overall Survival According to Pretreatment Prognostic Risk Factors and HTN Status

A multivariable analysis that included MSKCC risk factors (24) and other variables (25) indicated that treatment-induced HTN remained a statistically significant predictor of survival benefit ($P < .001$) regardless of how HTN was defined (Table 4) and regardless of potential confounding influences. Potential confounders included other prognostic markers for PFS (ECOG PS, time from diagnosis to treatment, age, platelet count, and lactate dehydrogenase) and for OS (ECOG PS, time from diagnosis to treatment, lactate dehydrogenase, corrected calcium, platelet count, and antihypertensive drug at baseline; all Ps < .05). Other potential prognostic factors evaluated included sex, race, hemoglobin levels, prior nephrectomy, and absolute neutrophil count.



	Anti-HTN drug only			Dose reduction only			Both		
Month	N	S	95% CI	N	S	95% CI	N	S	95% CI
10	97	87.4%	(83.8 to 93.6)	67	79.8%	(69.5 to 86.9)	140	89.7%	(83.8 to 93.6)
20	70	72.1%	(62.5 to 79.6)	46	58.6%	(47.1 to 68.4)	101	71.7%	(63.7 to 78.1)
30	52	55.3%	(45.1 to 64.4)	37	49.6%	(38.3 to 60.0)	72	56.4%	(48.0 to 64.1)

	Neither			Without HTN		
Month	N	S	95% CI	N	S	95% CI
10	73	85.0%	(75.5 to 91.0)	38	43.5%	(33.0 to 53.5)
20	40	56.2%	(44.4 to 66.4)	15	21.4%	(13.1 to 31.0)
30	29	40.7%	(30.0 to 51.6)	5	8.2%	(3.2 to 16.0)

Figure 3. Kaplan–Meier estimates of overall survival (OS) by hypertension (HTN) control and status. HTN was defined by a maximum systolic blood pressure of at least 140 mm Hg (post-cycle 1, day 1). N = number at risk; NR = not reached; S = survival percent, with 95% confidence interval (CI) in parentheses.

Association of HTN With HTN-Related Complications

To understand the clinical significance of treatment-induced HTN, the incidence of cardiovascular, cerebrovascular, ocular, and renal adverse events of any cause at any grade or at grade 3 or higher in sunitinib-treated patients were evaluated in patients with and without HTN, as defined by a mean SBP of at least 140 mm Hg. Mean (and not maximum) BP measurements were chosen for the safety analyses because the elevation of BP over time would be more likely to affect end-organ function than elevation at just a single maximum time point. The overall incidence of cardiovascular, cerebrovascular, and ocular adverse events was low, and it was similar between patients in both groups (Table 5). However, patients with HTN had somewhat more renal adverse events than patients without HTN (any-grade severity: 5% vs 3%, $P = .013$; severity at grade 3 or higher: 3% vs 2%, $P = .045$). Similarly, patients with HTN had slightly more adverse events of any-grade severity for all renal failure preferred terms combined than patients without HTN ($P = .014$), although this difference was not statistically significant when events of grade 3 or higher severity were compared ($P = .155$).

The median duration of treatment was defined as the date of the first dose to either the date of the last dose plus 28 days, or the end-of-study date, whichever occurred first (although treatment-related adverse events could have been reported beyond this adverse event reporting period). Median duration of treatment was 42.4 (range 0.1–182) weeks for 1,045 patients with a mean SBP of at least 140 mm Hg and 38.4 (range 0.7–197) weeks for 3,374 patients with a mean SBP below 140 mm Hg.

Discussion

In this retrospective exploratory analysis of HTN as a biomarker of efficacy in more than 500 patients with metastatic renal cell carcinoma treated with sunitinib, which to our knowledge may be the largest such investigation to date, sunitinib treatment–induced HTN was associated with statistically significantly improved clinical outcome. These findings support the hypothesis that HTN may be a viable biomarker of antitumor efficacy in this patient population, although development of HTN during sunitinib treatment was neither necessary nor sufficient for clinical benefit in all patients. Median PFS and OS were more than fourfold longer for patients with HTN than for patients without HTN as defined by a maximum SBP of at least 140 mm Hg. In addition, ORR was more than six times greater in patients with HTN than in patients without HTN. Moreover, a Cox proportional hazards model, with the onset of HTN as a time-dependent covariate, demonstrated a statistically significant decrease in the relative risk of both disease progression and death in patients who developed HTN, as defined by maximum SBP (and in the relative risk of death but not disease progression, with HTN defined by maximum DBP). Importantly, landmark analyses of HTN onset by the end of the first or second treatment cycle were also associated with improved clinical outcome. These data, combined with a multivariable analysis of baseline prognostic factors that showed that HTN (particularly systolic-defined HTN) was a statistically significant predictor of clinical outcome, provide further support to the growing body of evidence that VEGF pathway inhibitors are associated with treatment-induced HTN, which, in turn, may be a correlative biomarker of antitumor efficacy.

Table 4. Multivariable analysis of hypertension (HTN) status as a predictor for progression-free and overall survival (post-cycle 1, day 1)*

Variable	Progression-free survival				Overall survival			
	Maximum SBP ≥140 mm Hg (n = 442) vs <140 mm Hg (n = 92)		Maximum DBP ≥90 mm Hg (n = 363) vs <90 mm Hg (n = 171)		Maximum SBP ≥140 mm Hg (n = 442) vs <140 mm Hg (n = 92)		Maximum DBP ≥90 mm Hg (n = 363) vs <90 mm Hg (n = 171)	
	HR (95% CI)	*P*†	HR (95% CI)	*P*†	HR (95% CI)	*P*†	HR (95% CI)	*P*†
Treatment-induced HTN (yes vs no)	0.241 (0.180 to 0.323)	<.001	0.553 (0.443 to 0.690)	<.001	0.284 (0.216 to 0.374)	<.001	0.516 (0.408 to 0.651)	<.001
Age (<65 vs ≥65 y)	—	—	1.353 (1.083 to 1.690)	.008	—	—	—	—
ECOG PS (0 vs 1 or 2)‡	0.786 (0.636 to 0.971)	.026	0.763 (0.616 to 0.945)	.013	0.606 (0.478 to 0.767)	<.001	0.616 (0.486 to 0.781)	<.001
Time from diagnosis to treatment‡ (<1 vs ≥1 y)	1.308 (1.068 to 1.601)	.009	1.290 (1.052 to 1.582)	.014	1.687 (1.342 to 2.121)	<.001	1.631 (1.298 to 2.050)	<.001
LDH (>1.5 × ULN vs ≤1.5 × ULN)‡	1.751 (1.092 to 2.808)	.020	1.703 (1.057 to 2.742)	.029	1.686 (1.029 to 2.763)	.038	1.796 (1.106 to 2.917)	.018
Platelet count (>ULN vs ≤ULN)	2.182 (1.586 to 3.000)	<.001	2.266 (1.650 to 3.111)	<.001	2.035 (1.486 to 2.787)	<.001	2.283 (1.673 to 3.116)	<.001
Corrected calcium‡ (>10 vs ≤10 mg/dL)	—	—	—	—	1.938 (1.288 to 2.916)	.002	1.890 (1.253 to 2.852)	.002
Anti-HTN drug at baseline (yes vs no)	—	—	—	—	0.755 (0.592 to 0.963)	.024	0.725 (0.570 to 0.922)	.009

* Hypertension was defined as a maximum SBP of at least 140 mm Hg or a maximum DBP of at least 90 mm Hg. For binary variables, a hazard ratio less than 1 represents risk reduction for the first category and a hazard ratio greater than 1 represents risk reduction for the second category. CI = confidence interval; DBP = diastolic blood pressure; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; LDH = lactate dehydrogenase; SBP = systolic blood pressure; ULN = upper limit of normal.

† *P* values are from a two-sided log-rank test.

‡ Prognostic factors included in Memorial Sloan-Kettering Cancer Center risk-group stratification (24).

The incidence of HTN-associated adverse events in nearly 5000 sunitinib-treated patients with metastatic renal cell carcinoma was low and was generally similar between patients in this study who did and did not develop HTN (defined as mean SBP of at least 140 mm Hg), supporting the acceptability of HTN as a biomarker of efficacy. This is testimony to the general tolerability and manageability of this adverse event through standard antihypertensive therapy and/or dose schedule modification; however, patients with HTN had a slightly higher incidence of renal adverse events than patients without HTN. This mirrors a recently reported systematic review of the published literature by Zhu et al. (26) that found a notably increased risk for high-grade HTN (relative risk [RR] = 22.72; $P < .001$) but only a small increased risk for renal dysfunction (RR = 1.36; $P < .001$) in patients treated with sunitinib compared with control subjects (the majority of whom had renal cell carcinoma or gastrointestinal stromal tumor). In addition, a recent study by Launay-Vacher et al. (27) found that renal function (as assessed by glomerular filtration rate) in patients with renal cell carcinoma who received antiangiogenic therapy after unilateral nephrectomy declined over time (more so in patients who had HTN before initiation of therapy). However, it is unclear whether the apparent differences in adverse events in our study (recorded as kidney system organ class any-grade and grade 3 or higher; and combined renal failure, any-grade but not grade 3 or higher) are clinically important. This potential risk warrants additional prospective investigation.

These data and the potential for renovascular complications underscore the importance of monitoring patients with metastatic renal cell carcinoma for sunitinib-induced HTN and treating them as necessary with antihypertensive medication, as recently recommended by an expert panel of the National Cancer Institute for patients receiving VEGF inhibitors (28). Management of HTN may or may not include dose reduction, taking into account the findings reported herein that use of antihypertensive agents did not reduce sunitinib antitumor activity. Similarly, a prospective study of HTN management in patients with solid tumors who received the potent and selective VEGF inhibitor, cediranib, found that "antihypertensive prophylaxis" did not reduce the tumor response despite reducing the incidence of severe HTN (29). In addition, studies have shown that aggressive BP monitoring and treatment for HTN via use of a prespecified algorithm, rather than commonly used toxicity criteria, may achieve uninterrupted full-dose therapy with sunitinib (30) thus further improving the opportunity for improved clinical outcome. Use of HTN as a biomarker of efficacy may complement such a management approach, providing evidence of antitumor efficacy without appreciable increased risk of HTN-associated complications, thereby optimizing the therapeutic benefit of sunitinib.

The mechanism by which sunitinib and other antiangiogenic agents induce HTN requires further elucidation, but several studies have begun to shed light on this question. For example, antagonism of VEGF has been shown to decrease nitric oxide production, leading to a constriction of the vasculature and a reduction in sodium ion renal excretion, resulting in HTN (31,32). Furthermore, a recent study found that sunitinib treatment was associated with a statistically significant reduction of capillary density ($P < .01$) that was significantly correlated with changes in vessel

Table 5. Hypertension (HTN)-associated adverse events of any cause related to the brain, eye, heart, and kidney by HTN status*

	No. of patients (%)					
	Without HTN (n = 3374)		With HTN (n = 1045)		Total (N = 4917)†	
Adverse event	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any HTN-associated adverse event‡	300 (9)	116 (3)	112 (11)	46 (4)	439 (9)	177 (4)
Brain	13 (<1)	8 (<1)	7 (1)	3 (<1)	20 (<1)	11 (<1)
Cerebral hematoma	2 (<1)	1 (<1)	1 (<1)	0	3 (<1)	1 (<1)
RPLS	1 (<1)	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)
Transient ischemic attack	10 (<1)	6 (<1)	5 (<1)	3 (<1)	15 (<1)	9 (<1)
Eye	123 (4)	3 (<1)	40 (4)	1 (<1)	170 (3)	4 (<1)
Vision blurred	69 (2)	2 (<1)	14 (1)	0	84 (2)	2 (<1)
Vision acuity reduced	10 (<1)	1 (<1)	4 (<1)	1 (<1)	17 (<1)	2 (<1)
Visual disturbance	47 (1)	0	23 (2)	0	73 (1)	0
Visual field defect	3 (<1)	0	0	0	3 (<1)	0
Visual field defect NOS	1 (<1)	0	0	0	1 (<1)	0
Heart	63 (2)	50 (1)	16 (2)	14 (1)	86 (2)	68 (1)
Cardiac failure	18 (1)	15 (<1)	9 (1)	8 (1)	30 (1)	24 (<1)
Cardiac failure congestive	12 (<1)	10 (<1)	3 (<1)	3 (<1)	15 (<1)	13 (<1)
Left ventricular dysfunction	17 (1)	11 (<1)	1 (<1)	0	20 (<1)	12 (<1)
Myocardial infarction	19 (1)	16 (<1)	3 (<1)	3 (<1)	24 (<1)	21 (<1)
Kidney§	116 (3)	61 (2)	54 (5)	30 (3)	184 (4)	103 (2)
Nephrotic syndrome	2 (<1)	1 (<1)	2 (<1)	2 (<1)	4 (<1)	3 (<1)
Proteinuria	43 (1)	12 (<1)	17 (2)	6 (<1)	60 (1)	18 (<1)
Proteinuria present	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Renal failure¶	44 (1)	26 (1)	27 (3)	12 (1)	81 (2)	47 (1)
Renal failure NOS¶	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Renal failure acute¶	30 (1)	21 (1)	11 (1)	10 (1)	46 (1)	34 (1)
Thrombotic microangiopathy	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Thrombotic thrombocytopenic purpura	2 (<1)	2 (<1)	1 (<1)	1 (<1)	3 (<1)	3 (<1)

* HTN was defined as mean systolic blood pressure of at least 140 mm Hg. NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NOS = not otherwise specified; RPLS = reversible posterior leukoencephalopathy syndrome.

† HTN status was missing for 498 patients, of whom 27 (5%) and 15 (3%) had any-grade and grade 3 or higher HTN-associated adverse events, respectively.

‡ The absence of a preferred term under each HTN-associated complication system organ class indicates the absence of a reported adverse event (Note: the general NCI CTCAE, version 3.0 guidelines for grading adverse event severity may have been followed for adverse event grades that the NCI CTCAE does not recognize as appropriate for that adverse event term).

§ Using Fisher exact test, a comparison between patients with vs without HTN was statistically significant ($P = .0129$) for kidney system organ class adverse events of any-grade severity and was also statistically significant for adverse events of grade 3 or higher severity ($P = .0451$).

¶ Using a two-sided Fisher exact test, a comparison between patients with vs without HTN was statistically significant ($P = .0136$) for all renal failure preferred terms combined of any-grade severity but was not statistically significant for renal failure of grade 3 or higher severity ($P = .1548$).

morphology (and increased SBP [$r = -.57$; $P < .05$] and DBP [$r = -.68$; $P < .01$]), both of which were statistically significantly associated with prolonged PFS ($P = .044$) (33). Additional evidence indicates involvement of other renovascular mechanisms (10).

It may be hypothesized that the susceptibility of normal blood vessels to VEGF blockade, leading to HTN, is linked to the susceptibility of tumor vessels to VEGF blockade, resulting in a more robust antiangiogenic effect in response to sunitinib treatment, and thus, an enhanced clinical outcome. The precise mechanism(s) whereby VEGF inhibition leads to HTN and, further, the best means to exploit those mechanisms for clinical benefit in metastatic renal cell carcinoma and other tumor types requires additional investigation. Antihypertensive medication use at baseline remained statistically significantly associated with OS in the multivariable model, independent of other factors, including treatment-induced HTN. Also, the addition of antihypertensive medication did not adversely affect the favorable clinical outcome for hypertensive patients. These data further support the hypothesis that this phenomenon is a host effect. That is, inherent host biology (which predisposes one to both baseline and treatment-induced HTN) is intertwined with the biology of the antitumor effect of VEGF blockade, though the possibility that HTN itself predicts a more favorable outcome independent of the effect of VEGF inhibition cannot completely be excluded. The multiple hypotheses generated here warrant testing in prospective clinical trials to validate these findings and standardize the criteria for the use of HTN as a biomarker of VEGF pathway inhibitor efficacy.

There are several limitations of the current investigation. Such limitations include variability in BP characteristics among studies, lack of full pharmacokinetic data, and lack of consensus about which BP parameter is most reliably measured in this setting. Relative sunitinib dose intensity and cumulative sunitinib dose only weakly correlated with maximum BP in our analysis. In addition, a recently published pharmacokinetic–pharmacodynamic meta-analysis by Houk et al. (34) demonstrated a weak correlation ($r = 0.29$) between changes in DBP and trough plasma concentrations, indicating substantial interpatient variability in DBP elevation at given sunitinib trough plasma concentrations, in

predominantly patients with renal cell carcinoma and gastrointestinal stromal tumor (including patients from the two phase II metastatic renal cell carcinoma studies used in our analysis). However, further studies are warranted to confirm that sunitinib-induced HTN is a "true" biomarker of efficacy and not simply an epiphenomenon of higher drug exposure, a possibility that cannot be definitively excluded given the inherent limitations of a retrospective analysis.

The investigation into predictive biomarkers for response to antiangiogenic therapy is a high priority. Although these agents have broad antitumor activity, most notably as single agents in the treatment of metastatic renal cell carcinoma, there is, at present, no prospectively validated biomarker upon which to choose a specific therapy. The ideal biomarker would be simple, reflective of intended target inhibition, easy to measure, of low cost, and reliably present at baseline or early after initiation of therapy. Although several potential biomarkers have been recently investigated in renal cell carcinoma, including functional imaging, other treatment-related adverse events, circulating VEGF pathway proteins or endothelial cells, and VEGF single-nucleotide polymorphisms (35), none have been consistently associated with patient outcomes as demonstrated here. Furthermore, each of these modalities requires a substantial investment of patient resources, time, cost, and expertise. Therefore, because it is more manageable than other potential adverse event biomarkers, treatment-induced HTN, if prospectively validated, may best meet the criteria for a desirable biomarker in patients with advanced renal cell carcinoma treated with sunitinib.

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Notes

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