Original Study

Therapy of Treatment-Related Hypertension in Metastatic Renal-Cell Cancer Patients Receiving Sunitinib

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Abstract

Treatment-related hypertension (tHTN) during sunitinib treatment is common. We retrospectively analyzed in 72 sunitinib-treated metastatic renal-cell carcinoma patients risk factors for hypertension (tHTN) and the medical treatment of tHTN. Results suggested the efficient treatment of tHTN by calcium channel blockers and by an early combination of different anti-HTN drug classes.

Introduction: Treatment-related hypertension (tHTN) is frequent during sunitinib treatment. However, data on risk factors and treatment of tHTN remain scarce. **Patients and Methods:** Patients with metastatic renal-cell carcinoma treated with sunitinib from June 2004 to December 2011 were included. Medical records were retrospectively analyzed for tHTN risk factors and antihypertensive treatments (AHT). Descriptive statistics, Cox regression, and competitive risk models were applied. **Results:** A total of 51 (70.8%) of 72 patients developed tHTN after a median sunitinib treatment of 28 days. Mean blood pressure increased from 130/75 (range, 90 to 190/58 to 101) mm Hg on day 1 to 140/80 (range, 90 to 190/60 to 120, $P < .001$) mm Hg on day 28. Standard dose of sunitinib, age > 50 years, and prehypertension were identified as independent risk factors for tHTN. Thirty-eight patients (72.5%) in the tHTN subgroup received modification of AHT. Calcium channel blockers (CCB) were identified as the best at controlling tHTN compared to other drugs ($P = .045$). The combination of AHT was more potent than a dose increase of a single-drug AHT, and early AHT intervention was more efficacious than delayed start of therapy. **Conclusion:** Patients at risk for tHTN require more rigorous blood pressure measurement. CCB seemed to be most potent and efficient, and an early combination of different classes of AHT was more efficacious than full-dose, single-agent AHT.

Clinical Genitourinary Cancer, Vol. ■, No. ■, 1-11

Keywords: Adverse events of sunitinib, Antiangiogenic therapy, Antihypertensive therapy, Targeted therapy, VEGF inhibition

Introduction

Management of adverse events (AEs) during targeted therapies is crucial to optimizing patient outcomes.[1,2] Sunitinib was among the first approved targeted agents in metastatic renal-cell carcinoma (mRCC). The main target is vascular endothelial growth factor receptor (VEGFR) 2, a central receptor in tumor angiogenesis.[3] While inhibiting the tumor vasculature, the inhibition of vascular endothelial growth factor (VEGF) signaling in regular endothelial cells is associated with treatment-related hypertension (tHTN), a class-specific AE of VEGFR inhibitors. The incidence of tHTN varies from 17% to 76% among different VEGFR targeting agents.[4-6] A meta-analysis investigating 4999 patients treated with VEGFR inhibitors identified an incidence of 21.6% for low-grade and 6.8% for high-grade tHTN.[6] Respectively, a significantly increased relative risk for high-grade hypertension (HTN) during sunitinib treatment was reported (relative risk, 22.72 [95% confidence interval, 4.48-115.29, $P = .001$]).[7]

Cardiovascular risk factors are frequent in mRCC patients and may exaggerate cardiovascular AEs during mRCC treatment. Coronary artery disease, chronic heart failure, stroke, and other severe

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Submitted: Mar 25, 2016; Revised: Sep 24, 2016; Accepted: Oct 10, 2016

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1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2016.10.004

cardiovascular complications were observed during sunitinib treatment, and several other vascular complications have been reported for different VEGFR inhibitors.[5,6,8-10] Additionally, chronic kidney disease is a strong cardiovascular risk factor.[11] Therefore, anti–VEGF-treated mRCC patients need to be considered as a high-risk cohort for cardiovascular events. Although mainly preclinical studies have suggested direct cardiotoxicity of targeted agents, it remains controversial whether sunitinib is a direct cause of cardiovascular toxicity.[5,12-17] Recent analyses suggest that this effect might result from uncontrolled or undetected tHTN rather than from direct cardiotoxicity.[15,18]

Idiopathic arterial HTN has a high prevalence and therefore is a frequent comorbidity in cancer patients; in contrast, HTN during VEGFR inhibition remains less well defined.[19,20] Monitoring tHTN and implementing drug-based anti-HTN treatments (AHTs) are believed to be crucial to minimizing VEGFR inhibition–associated morbidity. Nonetheless, recommendations for supportive measures for tHTN during sunitinib treatment rely on expert opinions, which are mainly based on experience with idiopathic arterial HTN, with few observations during sunitinib therapy.[21,22] Therefore, we analyzed different risk factors for tHTN, the administered anti-HTN therapy, and their efficacy towards tHTN control in sunitinib-treated mRCC patients at our tertiary-care center.

Patients and Methods

Patient Characteristics, Oncologic Treatment, Blood Pressure, AHT, and AE Assessment

mRCC patients treated with sunitinib at our center during June 2004 and December 2011 were eligible for analysis. Patients with incomplete documentation of cardiovascular comorbidity or blood pressure (BP) measurement were not eligible for analysis. Last follow-up was in April 2014. In concordance with local ethic committee standards and according to the Declaration of Helsinki, medical charts were retrospectively analyzed in an anonymous manner.

The following cardiovascular risk factors were assessed: family history for coronary artery diseases and arterial HTN, previously diagnosed HTN or pre-HTN (defined as systolic BP [BPS] $\geq$ 120-139 mm Hg and $<$ 140 mm Hg; diastolic BP [BPD] $\geq$ 80-89 mm Hg and $<$ 90 mm Hg [according to Seventh Report of the Joint National Committee (JNC 7) criteria]),[23] clinical signs or diagnosed coronary artery disease or myocardial infarction, clinical signs or diagnosed chronic heart failure, documented severe valve malfunction, atrial fibrillation, current or past smoking, lipid metabolism alteration (hypertriglyceridemia, hypercholesterinemia), diabetes mellitus, diminished renal function, body mass index (BMI), sleep apnea disorder, and drug history (anti-HTN agents, and cardiovascular comedication [eg, aspirin, warfarin, antiarrhythmic agents, statins]).

Sunitinib was administered after written informed consent was obtained according to summary of product characteristics and continued until death, tumor progression, or unacceptable toxicity. Visits were performed on days 1, 14, and 28 at course 1, and routinely on day 1 and/or on day 28 of each consecutive course. Tumor assessment was performed every 3 months. Electrocardiogram was performed at baseline and whenever clinically indicated. Further cardiac diagnostic measurements were performed if clinically indicated. BP was measured at each visit. After the first 4 sunitinib-treated patients were assessed at our center, subsequent patients were instructed to measure their BP at home every day. These recorded ambulatory BP diaries were routinely checked at each visit. Patients were instructed to inform the treating physician if BP exceeded 140/90 mm Hg or if an AE occurred.

A BP of $>$ 140/90 mm Hg during sunitinib treatment was considered as tHTN (tHTN = BPS $\geq$ 140 mm Hg or BPD $\geq$ 90 mm Hg [according to JNC 7 criteria]) after being recorded at different time points, irrespective whether the assessment was performed at home or in the clinic.[23] Once tHTN was diagnosed by the treating physician, a drug-based anti-HTN therapy was initiated or a preexisting anti-HTN therapy dosage was increased; both were considered to be first-step anti-HTN therapy. Inadequate control of tHTN by first-step anti-HTN therapy was defined either by recurrence of tHTN or subsequent lack of response to first-step anti-HTN therapy. Failure of first-step anti-HTN therapy led to a second-step modification, which consisted of either adding another anti-HTN drug class or increasing the dose of an already administered anti-HTN therapy. Subsequent recurrence of tHTN and subsequent anti-HTN therapy modification were defined and administered corresponding to first- and second-step anti-HTN therapy. Administered drugs included β-blockers, calcium channel blockers (CCB; only dihydropyridine CCBs), angiotensin II receptor blockers, or angiotensinogen-converting enzyme inhibitors, with both considered to be angiotensin system inhibitors [ASI]. Time to normotension (BP $<$ 140/90 mm Hg) and time to failure of BP control (recurrence of BP $>$ 140/90 mm Hg) were assessed at each step of anti-HTN therapy modification. Assessed BP outliers were defined as HTN stage II (according to JNC 7; BP $\geq$ 160/100 mm Hg).[23]

Cardiovascular AEs or AEs that hinted at symptoms of HTN were assessed and defined as follows: HTN, headache and dizziness (without evidence of central nervous system metastasis), epistaxis (without evidence of thrombocytopenia), impaired vision (without evidence of central nervous system metastasis), cardiac palpitation, chest pain (clinically considered as cardiac origin), signs of chronic heart failure (according to the European Society of Cardiology 2008 guidelines), vascular complication (eg, wound healing, aortic aneurism), and cerebral vascular complications (eg, cerebral insult). Grading was performed according to Common Terminology Criteria for Adverse Events (CTCAE) 4.03.

All assessed risk parameters, AEs, and BP boards were defined before data assessment and analyses were initiated.

For comparison of doses and drug class efficacy of an anti-HTN therapy, the corresponding drug index (DI) and drug score (DS) were calculated. DI allows comparison of doses of different anti-HTN agents: DI = 10 $\times$ (daily dose/maximum recommended dose). The DS allowed the comparison of anti-HTN drug combinations (DS = sum of different DI of each step of anti-HTN therapy). The DI and DS were evaluated at baseline, at each step of modification of the anti-HTN therapy, and at the end of sunitinib treatment.[24]

Statistical Analysis

Means with standard deviations and medians with ranges were calculated. Subgroups were compared by appropriate testing by independent Student's t test, Mann-Whitney U test, or chi-square test, as well as by Pearson's correlation analyses. For multivariate binary logistic regression, age was coded as a binary variable on the basis of age distribution and the most robust age cutoff at univariate

Table 1 Characteristics of CVD Risk Factors in Sunitinib-Treated Metastatic Renal-Cell Carcinoma Patients by Occurrence of tHTN

Characteristic	All Eligible Patients	tHTN Patients	Non-tHTN Patients	*P*
Patient Characteristics				
Eligible patients	72 (100)	51 (70.8)	21 (29.2)	<.001
Sex				
Male	49 (68.1)	34 (66.7)	15 (71.4)	.649
Female	23 (31.9)	17 (33.3)	6 (28.6)	.649
Age, Years				
Median (range)	62.5 (39-82)	63.0 (44-82)	60 (39-80)	.162
Male, median (range)	63 (39-82)	62.96 (44-82)	64 (39-79)	.249
Female, median (range)	61 (42-80)	64 (48-79)	46 (42-80)	.348
ECOG PS				.065
0	62 (86.1)	46 (90.2)	16 (76.2)	.281
1	8 (11.1)	3 (5.9)	5 (23.8)	.087
≥2	2 (2.8)	2 (3.9)	0 (0)	.357
Nephrectomy	67 (93.1)	47 (90.1)	20 (95.2)	.197
Previous Oncologic Therapy				.136
None	35 (48.6)	28 (54.9)	7 (33.33)	.096
Immunotherapy (IL-2/IFN)	29 (40.3)	19 (37.26)	10 (47.62)	.452
Immunotherapy + chemotherapy	1 (1.4)	1 (1.96)	0 (0)	.518
TKI (sorafenib)	3 (4.2)	1 (1.96)	2 (9.525)	.150
Other	4 (5.5)	2 (3.92)	2 (9.525)	.346
Treatment interruption before sunitinib, days, median (range)	30 (0-2112)	26 (2-2112)	51.5 (0-676)	.648
Sunitinib Treatment				
Therapeutic line of administration, median (range)	2 (1-6)	2 (1-6)	2 (1-4)	.114
Treatment duration, months, median (range)	8.43 (0.5-33.13)	10.7 (0.53-33.13)	5.6 (30-27.7)	.053
Initial dose 50 mg OD 4/2	64 (88.9)	48 (94.1)	16 (76.2)	.028
Initial dose 37.5 mg OD 4/2	8 (11.1)	3 (5.9)	5 (23.8)	.028
Dose reduction during treatment	23 (31.9)	19 (37.3)	4 (19.0)	.193
cPFS, months, median (95% CI)	8.3 (4.7-12)	11 (8.3-13.8)	5.5 (2.8-9)	.018
Death/survival	29 (37.9)	18 (35.3)	11 (52.4)	.442
OS, months, median (95% CI)	23.6 (14.7-32.4)	28.4 (18.4-38.4)	17.3 (15.1-19.5)	.306
CVRF				
Cardiovascular Drugs				
Patients with CVD drugs[a]	35 (48.6)	28 (54.9)	7 (33.3)	.615
Median no. of CVD drugs	1 (0-6)	1 (0-6)	0 (0-4)	.598
Patients with AHT medication	35 (48.6)	29 (56.9)	6 (28.5)	.042
Drug score of AHT, mean ± SD	4.9 ± 9	6.1 ± 10.1	2.2 ± 4.7	.099
Patients with cardiac drugs	11 (15.3)	7 (13.7)	4 (19)	.575
HTN				
Diagnosed HTN before sunitinib	39 (54.1)	31 (60.8)	8 (38.1)	.079
Pre-HTN	27 (37.5)	24 (47.1)	3 (14.3)	.009
CVD History/CVRF				
Median no. of CVRF	1 (0-5)	1 (0-5)	1 (0-4)	.576
eGFR before TKI (mL/min)	70 (13-129)	69.9 (13-129)	75 (39-122)	.702
eGFR before TKI <60 mL/min	24 (33.3)	18 (35.3)	6 (28.3)	.63
BMI				.357
Low-weight BMI (<18.5 kg/m^2)	4	2	2	.243
Normal-weight BMI (18.5-24.9 kg/m^2)	27	22	5	.289
High-weight BMI (>25-29.9 kg/m^2)	36	26	10	.6
NA	5 (7)	1 (2)	4 (19)	

Table 1 Continued

Characteristic	All Eligible Patients	tHTN Patients	Non-tHTN Patients	*P*
Positive cardiac history[b]	43 (59.7)	34 (66.7)	9 (42.9)	.06
Smoking[c]	17 (23.6)	13 (25.5)	4 (19)	.558
NIDDM	13 (18.1)	8 (15.7)	5 (23.8)	.415
Lipid metabolism alteration[d]	11 (15.3)	7 (13.7)	4 (19)	.56

Data are presented as n (%) unless otherwise indicated.
Abbreviations: AHT = antihypertensive treatment; BMI = body mass index; CI = confidence interval; cPFS = progression based on radiologic or clinical evidence; CVD = cardiovascular disease; CVRF = cardiovascular disease risk factors; ECOG PS = Eastern Cooperative Oncology Group performance status; eGFR = estimated glomerular filtration rate; HTN = hypertension; IFN = interferon; IL = interleukin; NA = not applicable; NIDDM = non-insulin-dependent diabetes mellitus; OD = once daily; OS = overall survival; tHTN = treatment related hypertension; TKI = tyrosine kinase inhibitor.
[a]Antihypertensive therapy, oral anticoagulation (aspirin or coumadin) due to CVD, medication for alteration of lipid metabolism.
[b]Diagnosed hypertension, AF/palpitation, clinical signs or evidence of coronary artery disease and congestive heart failure, cardiac valve malfunction, prior myocardial infarction.
[c]Current or past smoking.
[d]Hypercholesterinemia and/or hypertriglyceridemia.

analysis. Variables of $P < .2$ from comparison of subgroups were included in univariate binary logistical regression analyses. Variables with a $P < .07$ at univariate analyses were included in the primary multivariate logistical regression. The multivariate logistical regression analysis, using a stepwise exclusion model, was confirmed by a stepwise inclusion model to identify risk factors for tHTN. Correlating parameters ($R > 0.7$) or parameters that reflected similar features were excluded. Secondary adjusted multivariate analysis was performed. Therefore, the parameter of comorbidity without correlation with identified independent risk parameters for tHTN from the primary multivariate analysis was administered for adjustment.

Progression-free survival (defined as clinical PFS: time of radiologic or clinical evidence of progression) and overall survival (OS) were estimated by Kaplan-Meier analysis, using the log-rank method for subgroup comparison. In the absence of death, or in the case of patients lost to follow-up, the end point was censored. The duration of follow-up was calculated from the date of first-line systemic treatment to the date of death or last known follow-up. SPSS 23.0 software (IBM SPSS, Chicago, IL) and "R" (www.r-project.org) was used for statistical assessment. Two-sided *P* values of $< .05$ were considered statistically significant.

The potency of different anti-HTN agents for treatment of tHTN was analyzed by a competitive risk model.[25,26] The time-dependent failure probability of control of tHTN (tHTN control = BPS < 140 and/or BPD < 90 mm Hg) was estimated for each anti-HTN drug class. The time point where failure probability was 50% was defined as time to treatment failure (TTF). To avoid bias from combined anti-HTN drug effects, a subgroup of patients receiving only a single-agent anti-HTN therapy was analyzed (either anti-HTN drugs that were preexisting at baseline and maintained during sunitinib treatment or that were newly initiated during sunitinib treatment; n = 39).

Results

mRCC Patient Characteristics

Within the observation period, 146 mRCC patients received sunitinib at our outpatient clinic. Because a high proportion of the patients were seen only once for consultation, and because medical records had incomplete BP measurement or record of cardiovascular risk factors, only 72 patients from the observation period were eligible for the analysis. However, all sunitinib-treated patients within the observation period were assessable for oncologic baseline parameters and treatment outcome. Comparison of those parameters among patients eligible or ineligible for the retrospective study revealed hardly any significant differences even though OS was better among patients ineligible for analysis (Supplemental Table 1 in the online version).

Baseline characteristics, parameters regarding cardiovascular disease risk factors, and data on oncologic treatment were assessed in the study cohort and compared between patients with and without tHTN (Table 1). Characteristics and cardiovascular risk factors were largely similar. However, compared to patients without tHTN, patients with tHTN showed significantly longer clinical PFS (log rank: $P = .018$), a trend for better performance status ($P = .065$), longer sunitinib exposure ($P = .053$), higher initial sunitinib dosing ($P = .028$), and lower frequency of sunitinib dose reductions ($P = .193$) (Table 1). Among the cardiovascular risk factors, preexisting anti-HTN therapy ($P = .042$) and pre-HTN ($P = .009$) at baseline and/or before initiation of sunitinib treatment were significantly more frequent among patients with tHTN. Also, patients within the tHTN subgroup showed a trend for a more frequent positive cardiac history ($P = .06$) (Table 1).

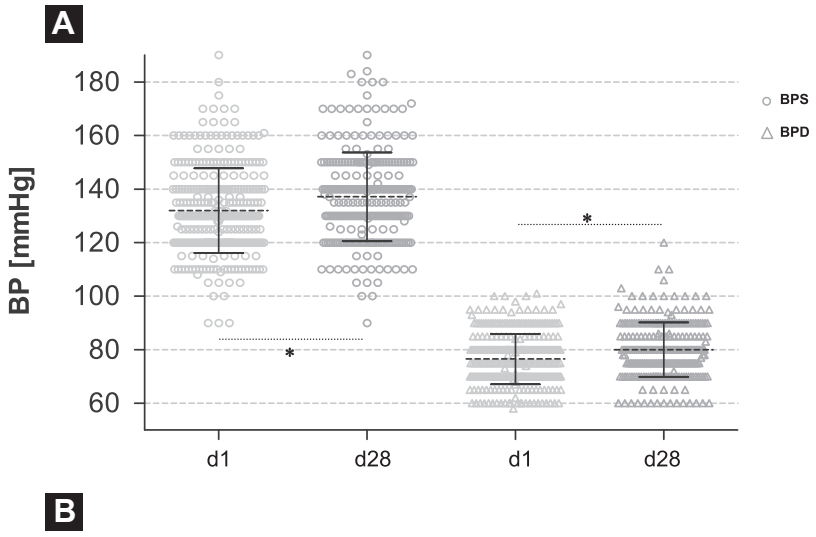
tHTN in mRCC Patients During Sunitinib Therapy

After a median duration of 28 (range, 0-213) days of sunitinib treatment, in 70.8% (n = 51) of the patients, tHTN was identified. Comparison of all evaluable BP values for each day 1 with values for each day 28 of all subsequently administered sunitinib cycles revealed a significant rise in BP. Furthermore, both BPS and BPD increased significantly (P BPS $< .001$; P BPD $< .001$) (Figure 1A). Among the subgroups, gain in BP was significant in patients with tHTN (P PBS $< .001$; P BPD $< .001$), while patients without tHTN showed no significant increase in BP (Figure 1B). This was in line with our finding that only patients in the tHTN group had BP outliers, which occurred predominantly within the first 4 courses of sunitinib treatment (63% of all BP outliers).

Analyses of Risk Factors for tHTN

A binary logistical regression analysis was performed to identify risk factors for tHTN. Nine parameters associated with tHTN were identified in the univariate analysis (Table 2). In the primary unadjusted multivariate analysis, age > 50 years, sunitinib starting

Figure 1 Course of Blood Pressure During Sunitinib Treatment in Metastatic Renal-Cell Carcinoma Patients (A) Seventy-Two Patients Completed At Least One Course of Sunitinib (Longest Follow-Up 18 Courses), and BPS and BPD Increased Significantly From All Day 1 (d1) (n = 338) To All d28 (n = 274) of All Subsequent Courses (*P < .001). Mean Values and Standard Deviations are Shown. (B) Illustrations of Corresponding BPS and BPD Values in Dependence of Subgroups Either With or Without tHTN



	d1	d28	p
All pts.			
BPS mmHg, mean (range)	130 (r: 90-190)	140 (r: 90-190)	<0.001
BPD mmHg, mean (range)	75 (r: 58-101)	80 (r: 60-120)	<0.001
tHTN pts			
BPS mmHg, mean (range)	130 (r: 100-190)	140 (r: 90-190)	<0.001
BPD mmHg, mean (range)	76.5 (r: 58-101)	80 (r: 60-120)	<0.001
non-tHTN pts.			
BPS mmHg, mean (range)	120 (r: 90-140)	120 (r: 100-140)	0.1
BPD mmHg, mean (range)	70 (r: 60-90)	80 (r: 60-120)	0.325

Abbreviations: BPD = diastolic blood pressure; BPS = systolic blood pressure; tHTN = treatment-related hypertension.

dose of 50 mg once daily (4/2 regimen), and pre-HTN at baseline were identified as independent risk factors for tHTN occurrence in sunitinib-treated patients (Table 2). Adjusted secondary multivariate analysis for gender, diabetes, smoking, and alterations of lipid metabolism identified similar independent risk factors for tHTN (Supplemental Table 2 in the online version).

Characteristics and Efficacy of Administered Anti-HTN Therapy for Treatment of tHTN

The administered anti-HTN therapies in patients with tHTN significantly reduced the BPS and BPD (Figure 2A). Analysis of all steps of anti-HTN therapy modifications revealed that the BP significantly increased within the tHTN subgroup ($P \leq .001$) before anti-HTN therapy modification and significantly declined ($P \leq .001$) after modification of anti-HTN therapy for both BPS and BPD (Figure 2A). Significant findings were also found when first-step anti-HTN therapy modification was analyzed (Figure 2B). Similar trends were seen for the second and further subsequent steps of modifications of anti-HTN therapy (data not shown).

Throughout the sunitinib treatment, 70.8% (n = 51) of all patients received an anti-HTN therapy. Only 6 patients in the non-tHTN subgroup received an anti-HTN therapy. In patients with tHTN, 72.5% (n = 38 of 51) received at least one modification of the anti-HTN therapy at a median of 3 (range, 0-52) days after detection of tHTN. The occurrence of tHTN was frequently associated with the failure of a preexisting anti-HTN therapy (n = 22, 62.8%).

Overall, anti-HTN drug modification (a new agent or an increased dose of an existing agent) was administered 64 times in patients with tHTN. CCB were thus predominantly administered (Table 3). The characteristics and efficacy of the preexisting baseline anti-HTN therapy and of each step of drug modification in the tHTN patients are listed in Tables 3 and 4.

Modification of anti-HTN therapy was significant only in patients with tHTN. The DS of the anti-HTN therapy at baseline revealed no significant differences among patients with and without tHTN (P = .099, Table 1). The average DS was significantly increased during sunitinib treatment in patients with tHTN (baseline: 6.1 ± 10.1; end of sunitinib: 12.8 ± 11.1, P < .001). Among patients without tHTN, the average DS was not significantly increased within the course of sunitinib (baseline: 2.2 ± 4.7; end of sunitinib: 2.2 ± 4.6, P = .392). At the end of sunitinib

Table 2 Analysis of Risk Factors for tHTN During Sunitinib Treatment by Univariate and Multivariate Binary Logistical Regression

Parameter	*P*, tHTN versus Non-tHTN	Univariate Analysis		Multivariate Analysis	
		P	OR (95% CI)	*P*	OR (95% CI)
Patient Characteristics					
Age >50 years	.005	.008	5.66 (1.58-20.28)	.016	5.55 (1.38-22.40)
ECOG PS >0	.118	.129	0.35 (0.09-1.36)		
Prior oncologic therapy					
None	.096	.045	3.25 (1.03-10.31)		
Immunotherapy	.415	.453	0.67 (0.24-1.89)		
TKI	.150	.191	0.19 (0.02-2.27)		
Therapeutic line of sunitinib	.114	.129	0.66 (0.39-1.13)		
Starting dose sunitinib 50 mg	.028	.040	5.00 (1.07-23.3)	.019	8.56 (1.43-51.34)
Starting dose sunitinib 37.5 mg	.028	.040	0.20 (0.04-0.93)		
Sunitinib dose reduction	.193	.200	2.29 (0.65-8.10)		
CVD Risk Factors (Baseline)					
Prior anti-HTN therapy	.042	.033	3.3 (1.10-9.87)		
Prior HTN	.079	.083	2.52 (0.89- 7.16)		
Pre-HTN	.009	.014	5.33 (1.4-20.37)	.031	5.07 (1.16-22.24)
Positive cardiac history	.061	.065	2.27 (0.94-7.56)		
BP Values					
BPS, sunitinib baseline	.014	.021	1.06 (1.01- 1.11)		
BPD, sunitinib baseline	.325	.321	1.04 (0.97-1.11)		

Abbreviations: BPD = diastolic blood pressure; BPS = systolic blood pressure; CI = confidence interval; CVD = cardiovascular disease; ECOG PS = Eastern Cooperative Oncology Group performance status; HTN = hypertension; OR = odds ratio; tHTN = treatment-related hypertension; TKI = tyrosine kinase inhibitor.

treatment, the DS was significantly higher among patients with tHTN compared to patients without tHTN ($P < .001$).

We then analyzed tHTN patients with de novo single-agent anti-HTN therapy only (n = 15 out of 51). We found that anti-HTN therapy was provided at a median of 13 (range, 0-40) days after tHTN occurrence, which resulted in normotension at a median of 20 (range, 1-59) days. Time to initiation of anti-HTN therapy and time to normotension (BPS/BPD < 140/90 mm Hg) were positively correlated (Pearson's $R = 0.907$, $P = .005$). The severity of BP, once an anti-HTN therapy was initiated (HTN stage I, or HTN stage II according to JNC 7 criteria), did not greatly affect control of tHTN.

Potency of Administered Anti-HTN Therapy for Treatment of tHTN

The potency of different anti-HTN agents regarding control of tHTN was analyzed by a competitive risk model. TTF of an anti-HTN therapy to control tHTN was estimated (Figure 2C). The TTF of all anti-HTN drugs (n = 39, patients with single-agent anti-HTN therapy) was 67.5 days. CCB (n = 19) were the most frequently administered, with a TTF of 200 days, which was significantly longer compared to all other single-agent therapies (n = 20, $P = .0379$). Also, we evaluated whether the potency of each anti-HTN substance depended on its therapeutic mechanism. CCB (n = 19, TTF = 200 days) were more potent ($P = .045$) than diuretics (n = 4, TTF = 30 days), β-blockers (n = 11, TTF = 15 days), and ASI (n = 5, TTF = not reached).

To compare the effect of different anti-HTN therapies dosages, the impact of DI on the TTF was calculated. Within the single-agent anti-HTN therapy group, a DI of ≤ 5 (reflecting the average DI of standard-dose single-agent anti-HTN therapy) (n = 33, TTF = 60 days) was compared to DI ≥ 5 (n = 7, TTF = 61 days); we found no significant difference in TTF, thus indicating that there was no significant impact of anti-HTN therapy dosage ($P = .721$).

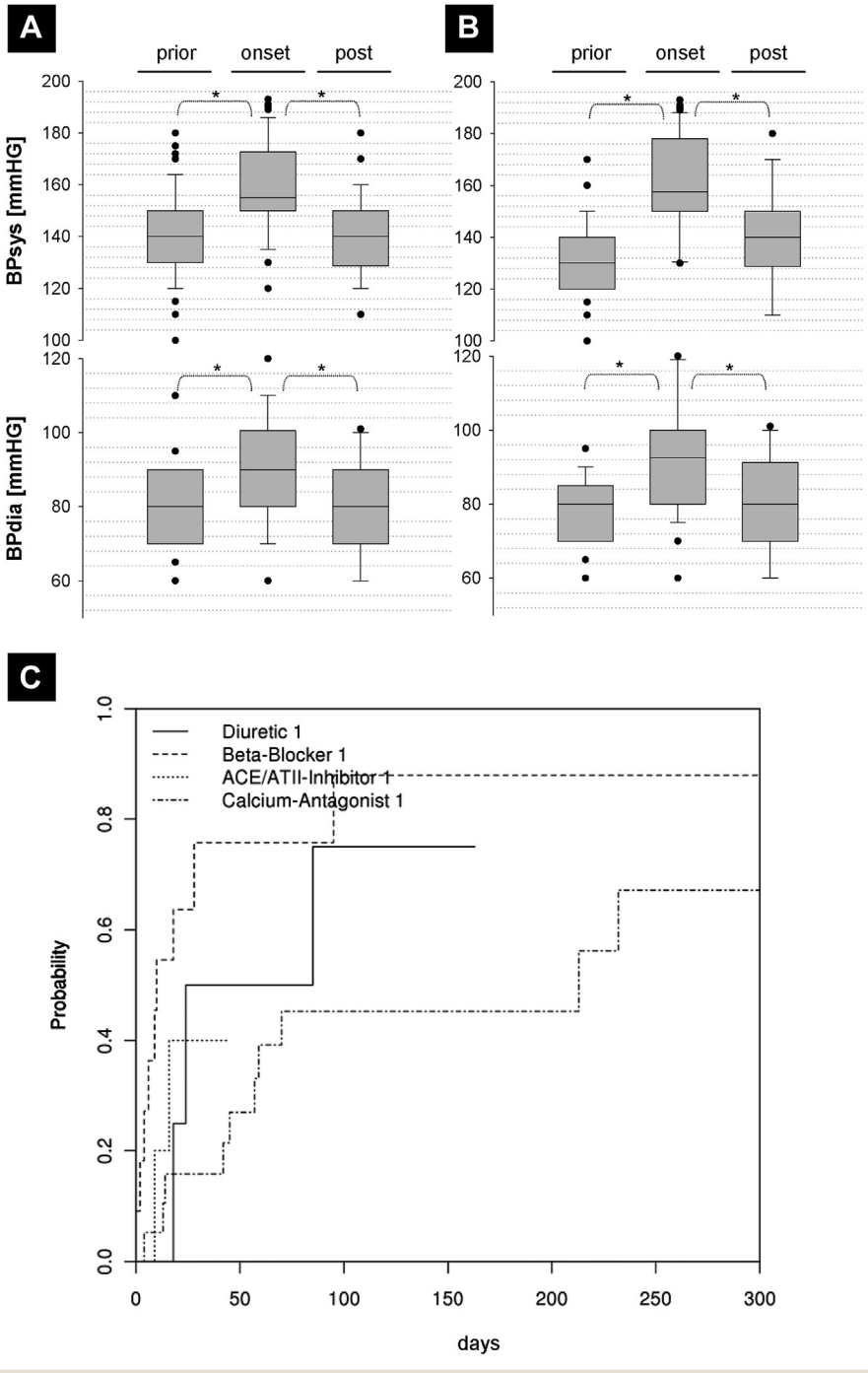
Cardiovascular AEs

Cardiovascular AEs during sunitinib treatment were assessed (Table 5). Overall, 124 cardiovascular AEs were found; of these, 34 were considered to be severe (CTCAE grade 3 or higher). The most frequent AEs were HTN itself, followed by clinical signs of chronic heart failure and epistaxis. Among the subgroups, most of the severe AEs occurred in the tHTN group (Table 5).

Discussion

tHTN is a class-specific AE of VEGFR inhibitors with a varying incidence among different agents. Furthermore, its incidence is artificially affected by the use of diverse HTN classifications, making it hard to compare data across different trials.[8,27,28] Most trials investigating VEGFR inhibitors applied CTCAE 3.0, where HTN is not as tightly defined as in the JNC 7 criteria or CTCAE 4.03. Analyses based on JNC 7 criteria or CTCAE 4.03 reported a far higher incidence of tHTN during VEGFR inhibition.[29-31] Therefore, the high rate of 70.8% of patients with tHTN during sunitinib treatment identified here is reasonable because we applied the JNC 7 criteria. We found that tHTN occurred predominantly within the first cycle of sunitinib administration, which is in line with previous reports.[4,32-34] Nonetheless, because of the high cardiovascular risk

Figure 2 **Efficacy and Potency of Administered AHT to Patients On tHTN. (A) BPS and BPD of All Evaluable Steps of AHT Modification (First Step AHT n = 38, Second Step AHT n = 16, Third to Fifth Step AHT n = 7, Total of 1- To 5-line AHT n = 61). Prior Indicates BP Value of Visit/Baseline Before tHTN Detection; Onset, BP Value At tHTN Onset; and Post, BP Value of Subsequent Visit After tHTN Detection (*$P \leq .001$). (B) Equal Tendencies Were Found For Patients Who Received First-Line AHT (n = 38) (*$P \leq .001$). (C) Competitive Risk Analyses Were Used To Compare Potency of Different AHT Substances in Subgroup of Single-Agent AHT Receivers, Which Illustrates Failure Probability of Different Substances To Control tHTN in Dependence of Time (BB n = 11, CCB n = 19, AT/Angiotensin-converting-enzyme Inhibitor n = 5, Diuretics n = 4)**



Abbreviations: ACE/ATI-inhibitor = AT/angiotensin-converting-enzyme-inhibitor; AHT = antihypertensive treatment; BB = β-blocker; BP = blood pressure; BPD = diastolic blood pressure; BPS = systolic blood pressure; tHTN = treatment-related hypertension.

Table 3 AHT During Sunitinib Treatment in Metastatic Renal-Cell Carcinoma Patients

Characteristic	All Eligible Patients, N	tHTN, N	Non-tHTN, N
AHT Drug Classes Initiated Before Sunitinib Treatment			
Diuretics	12	9	3
ACE inhibitor	10	7	3
β-Blocker	18	16	2
ARB	6	6	0
CCB	11	7	4
α-Blocker	1	1	0
AHT Drug Modifications After Sunitinib Treatment			
Diuretics	6	4	2
ACE inhibitor	4	4	0
β-Blocker	4	4	0
ARB	3	3	0
CCB	30	30	0
α-Blocker	2	2	0
Dose escalation of prior AHT	17	17	0

Numbers refer to numbers of patients receiving at least one AHT drug or modification.
Abbreviations: AHT = antihypertensive treatment; ARB = angiotensin II receptor antagonist; CCB = calcium channel blocker; tHTN = treatment-related hypertension.

burden of mRCC patients, demonstrated by the baseline parameters and prior reports, as well as the occurrence of a relevant proportion of BP outliers after 4 cycles of sunitinib treatment (38% of all BP outlier values), the current analysis suggests that regular ambulatory BP measurement is necessary throughout sunitinib treatment.[4,33-35]

The biological relevance and the etiology of tHTN remain controversial. In terms of OS and PFS, tHTN was thought to be a surrogate marker of response, even though this was never prospectively confirmed.[30,32] A pooled data analysis from a phase 2/3 trial of mRCC patients with carefully conducted landmark analysis found no relevant association between tHTN and PFS or OS.[36] Although not the primary focus of our analysis, we found an improved time to clinical progression in patients with tHTN. However, those patients also had a trend for longer sunitinib treatment, a higher initial dosage, and a better performance status. Nonetheless, a final conclusion between the association of tHTN and tumor response could not be drawn because of the small sample size.

Risk factors for tHTN during sunitinib treatment are not well characterized. In general, well-known risk parameters for arterial HTN were thought to be of relevance.[4,8,22] Surprisingly, we found a high percentage of HTN (54.5%) or pre-HTN (37.1%) at baseline in our study that was substantially higher than in previous reports, where the prevalence for HTN was only 37%.[19,37] Also, according to other cardiovascular risk factors, such as diminished estimated glomerular filtration rate, high BMI, and diabetes, identified incidences have to be considered in the current cohort as high, at least compared to a mixed cancer cohort treated with VEGF inhibitors.[31,38] This finding might reflect biological risk parameters for disproportional tHTN rates during sunitinib therapy in mRCC patients; on the other hand, HTN is supposed to be a risk factor in the etiology of renal-cell carcinoma.[37,39,40] Nonetheless, we identified pre-HTN at baseline, age > 50 years, and initial sunitinib dose of 50 mg OD to be independent risk factors for tHTN during sunitinib therapy. In terms of the impact of pre-HTN and age for tHTN occurrence, our findings match with a prior report analyzing a mixed cancer cohort treated with different VEGF inhibitors.[31,38]

Most recommendations of supportive measures for tHTN are based on experience with idiopathic HTN treatment strategies and mostly reflect expert opinion.[8,21,22,35] However, these strategies have not been systematically tested in sunitinib-treated mRCC patients. Additionally, the clinical usefulness of weight reduction, regular physical exercise, or a strict diet in advanced cancer patients, who have high comorbidity, pain, and fatigue, has yet to be demonstrated.[8] Therefore, in our experience, a drug-based AHT is of major importance. Here, 72.5% of all patients with tHTN (52.7% of all patients) received at least one drug-based anti-HTN therapy or modification of an existing anti-HTN therapy, which effectively controlled HTN, although often several steps of anti-HTN therapy modification were necessary. The high rate of administered anti-HTN therapies is also in line with 2 recent reports.[31,38] For the first time, our study showed the superior potency of CCB compared to other anti-HTN classes for the control of tHTN during sunitinib therapy, a finding that contradicts prior recommendations.[8,21,41] This suits also to the demonstrated potency of CCB during treatment with the experimental VEGFR inhibitor cediranib in both preclinical models and clinical trials.[42-45] However, because of CYP3A4 interaction with sunitinib,

Table 4 Initiated AHT Modifications in Patients With Occurrence of Treatment-Related Hypertension at Each Subsequent Step of AHT Drug Modification

Characteristic	Prior AHT	1st AHT	2nd AHT	3rd AHT	4th AHT	5th AHT	6th AHT
No. of patients receiving at least one AHT drug or AHT modification	35	38	16	5	3	1	1
Failed AHT, n (%)	22 (62.8)	16 (42.1)	5 (31.3)	3 (60)	1 (33.3)	1 (100)	0
Time to failure of AHT, days, median (range)	22 (0-213)	42.5 (0-241)	80 (5-247)	144 (18-268)	NA	NA	NA
Time to normotension, days, median (range)	NA	11 (1-198)	12.5 (1-75)	20 (5-35)	NA	NA	NA
DI, mean ± SD		5.5 ± 3	5.5 ± 2.3	4.3 ± 3.2	4.2 ± 1.4	6.6	5
DS, mean ± SD	4.91 ± 9	11.1 ± 10.8	14.3 ± 6.9	19.6 ± 7.4	22.5 ± 2.5	31.6	40

Prior AHT reflect AHT drug characteristics before initiation of sunitinib treatment.
Abbreviations: AHT = antihypertensive treatment; DI = drug index; DS = drug score; NA = not applicable.

Table 5 Cardiovascular AEs During Sunitinib Therapy in Metastatic Renal-Cell Carcinoma Patients

AE	All Eligible Patients		tHTN Patients		Non-tHTN Patients	
	Any Grade AE	Grade 3/4 AE	Any Grade AE	Grade 3/4 AE	Any Grade AE	Grade 3/4 AE
No. of all cardiovascular AEs	124	34	101	33	23	1
Hypertension	60 (83)	29 (40)	49 (96)	29 (57)	11 (52)	0 (0)
Chronic heart failure	15 (21)	0 (0)	12 (24)	0 (0)	3 (14)	0 (0)
Epistaxis	12 (17)	0 (0)	11 (22)	0 (0)	1 (5)	0 (0)
Headache	8 (11)	1 (1)	8 (16)	1 (2)	0 (0)	0 (0)
Dyspnea	8 (11)	1 (1)	5 (10)	0 (0)	3 (14)	1 (5)
Impaired vision	5 (7)	0 (0)	4 (8)	0 (0)	1 (5)	0 (0)
Dizziness	4 (6)	0 (0)	2 (4)	0 (0)	2 (10)	0 (0)
Chest pain	4 (6)	1 (1)	4 (8)	1 (2)	0 (0)	0 (0)
Palpitation	4 (6)	0 (0)	2 (4)	0 (0)	2 (10)	0 (0)
Vascular complication	2 (3)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
Pulmonary embolism	1 (1)	1 (1)	1 (2)	1 (2)	0 (0)	0 (0)
Cerebral insult	1 (1)	1 (1)	1 (2)	1 (2)	0 (0)	0 (0)

Shown are all considered cardiovascular AEs (according to CTCAE 4.03) of the analyzed cohort and the corresponding subgroups with and without tHTN.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; tHTN = treatment-related hypertension.

non-dihydropyridine CCB should be avoided.[2] Furthermore, diuretics demonstrated some additional activity in our analysis. Our analysis suggests that a combination of drugs with different mechanisms might be more potent than a dose intensification of a single-agent anti-HTN therapy. The high failure rate of BP control by a preexisting anti-HTN therapy indicates the role of preexisting HTN as a risk factor. In addition, early anti-HTN therapy intensification might foster better anti-HTN therapy efficacy, as illustrated by the correlation of time to anti-HTN therapy initiation at treatment-related tHTN onset and the time to normotension. Interestingly, prophylactic anti-HTN therapy with CCB had already safely been administered to cediranib-treated patients.[44] Therefore, because CCB were found to be effective and potent during sunitinib therapy, and considering that the early initiation of anti-HTN therapy might be important for tHTN control, early CCB treatment in patients with tHTN risk factors might be feasible.

ASI are thought to improve the outcome of cancer patients, including mRCC patients.[46-49] In particular, VEGFR inhibitor–treated mRCC patients are supposed to benefit the most from ASI administration in terms of improved OS as a result of potentially enhanced antitumor effects.[49] However, a recent large retrospective analysis of 1545 pooled patients could not confirm this effect of ASI in mRCC patients; furthermore, an exploratory analysis suggested a survival advantage by CCB.[50] Our cohort is too small to permit us to draw any conclusions regarding PFS or OS in terms of administering anti-HTN therapy (Supplemental Figure 1 in the online version), though our data suggest a low potency of ASI compared to other drug classes in terms of control of tHTN, even though this group was rarely administered. This is also in line with experimental findings.[45] Nonetheless, the potential higher potency of CCB to control tHTN compared to ASI is of importance, especially when taking into account the cardiovascular morbidity and mortality of mRCC patients.[13,51]

Although phase 3 trials on sunitinib have rarely reported on cardiovascular AEs, we found a moderate rate, which is also related to some extent by CTCAE 4.03.[52,53] In particular, the moderate rate of cardiovascular AEs was mainly reported in the tHTN group. Despite the frequency of clinical evidence of chronic heart failure, the frequencies we identified match to other reports focusing on cardiovascular AEs during VEGF inhibition.[16,17,32,38,54] However, when we compare prior reports, the frequency of chronic heart failure is surprisingly high, although nearly similar to a report by Hall et al.[16] However, it remains to be determined whether the administered anti-HTN therapy affected the incidence of cardiovascular AEs at all.

Our analyses are limitated by the study's retrospective design. Analyses reflect a selected patient cohort with subgroup analysis, warranting caution in interpreting the impact of our findings.[55] In particular, the predominantly administered CCB might cause an overestimation of its true efficacy in our statistical model.[55] In addition, incomplete medical records and patients lost to follow-up, thus ensuring analysis of only a part of patients within the observation period, may result in bias. Nonetheless, analyzing tumor and treatment characteristics of eligible and ineligible patients did not reveal any marked difference according to sunitinib treatment. Further, ambulatory home BP measurement relies on patient documentation and compliance, without external validation. This might reflect another bias, although ambulatory BP measurement has been considered precise and relevant; a phase 2 trial on axitinib demonstrated comparable precision of clinical and home BP measurement.[56,57]

However, to confirm our findings, which must be considered hypothesis generating, a prospective trial, or at least consideration of these matters in further anti-VEGFR trials, are needed.

Conclusion

The results of this study indicate that interesting hypotheses may be generated regarding the daily clinical routine during treatment with sunitinib in mRCC patients. An instruction in home-care BP monitoring is a key strategy for the early detection and treatment of

sunitinib-associated HTN. For patients at high risk of tHTN (age > 50 years, 50 mg sunitinib OD starting dose, or pre-HTN), routine and permanent BP monitoring should be considered. Early intervention for tHTN might be important when BP increases above the threshold of 140/90 mm Hg. In the absence of confounding factors (such as congestive heart failure), non-dihydropyridine CCB is the best way to quickly and reliably control tHTN. If control of tHTN is inadequate, an early combination of agents with different mechanisms of action may provide better control of tHTN.

Clinical Practice Points

- tHTN during sunitinib treatment in mRCC has been reported, with variable incidence.
- tHTN is believed to cause severe cardiovascular morbidity.
- Recommendations for assessment of patients at risk and optimal supportive measures for sunitinib-associated HTN are mainly based on expert opinion, rather than on data.
- Management of AEs is fundamental during the period of targeted therapy, to ensure optimal patient outcome.
- We identified patients aged > 50 years, patients receiving 50 mg 4/2 scheduled sunitinib, and patients with pre-HTN at baseline as being at particular risk for development of sunitinib-related HTN.
- CCB are better at controlling tHTN than other drug classes; in addition, early AHT seems to be more effective than delayed treatment.
- Once initiated, if anti-HTN medical treatment fails, an early combination of different drug classes seems to be more potent than dose escalation of an already initiated anti-HTN agent.
- The current findings may help clinicians focus on patients at an increased risk for tHTN, thus enabling a rapid, rational drug choice for effective anti-tHTN therapy as well as, if necessary, a feasible way to escalate AHT, potentially diminishing the risk of cardiovascular morbidity during sunitinib treatment in mRCC patients.
- Retrospective analysis, like that performed here, are hypothesis generating; further work on this topic is mandatory.

Acknowledgment

We are grateful for constructive discussion with Annika Grosshennig, Department of Biostatistics, Hannover Medical School.

Disclosure

P.I. received travel grants and lecture honoraria and advisory fees by Novartis, Bayer, Pfizer, BMS and GSK. V.G. received honoraria by Novartis, Pfizer, GSK, BMS. Advisory role: Novartis, Pfizer, GSK, BMS, MSD, Bayer. The other authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental tables and a figure accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clgc.2016.10.004.

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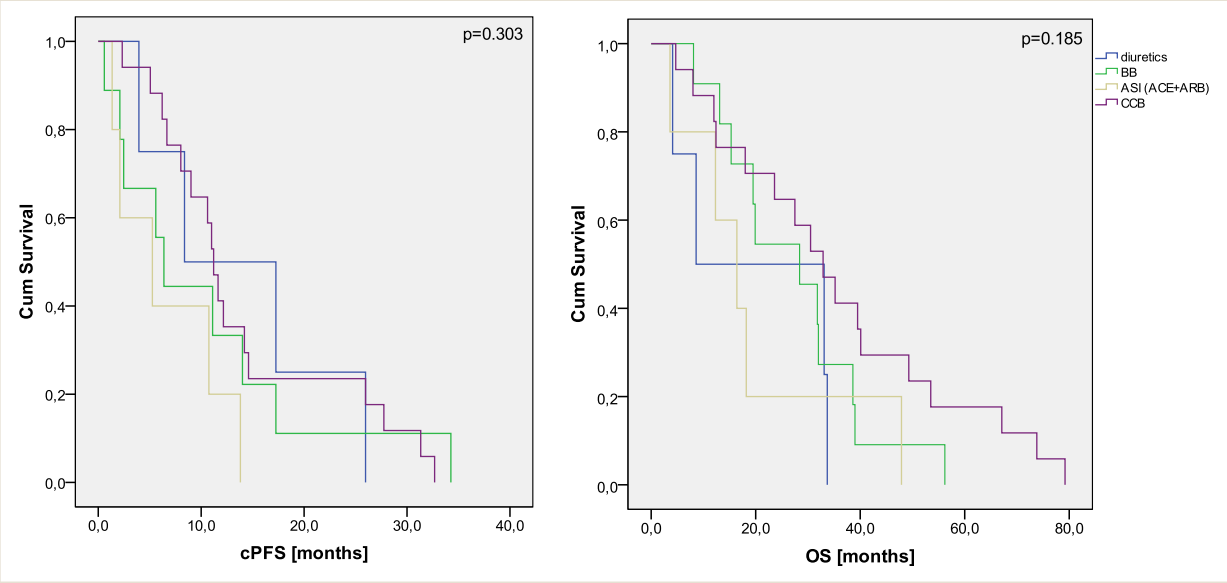
Supplemental Figure 1 **Subgroup Analysis of Clinical Progression-free Survival and Overall Survival of Metastatic Renal-Cell Carcinoma Patients Treated With Sunitinib. Subgroup Consisted of Patients With Treatment-Related Hypertension and Single-Agent Antihypertensive Therapy (cPFS: Overall: 10.8 [95% CI, 7.6-13.9] Months, Diuretics: 8.4 [95% CI, 0-21.4] Months, BB: 6.4 [95% CI, 4-8.7] Months, ASI 5.3 [95% CI, 0-12] Months, CCB: 11.2 [95% CI, 11.2 [95% CI, 9.8-12.6] Months, Log Rank *P* = .303; OS: Overall: 28.4 [95% CI, 14.2-42.6] Months, Diuretics: 8.6 [95% CI, 0-37] Months, BB: 28.4 [95% CI, 15.1-41.7] Months, ASI 16.4 [95% CI, 7.6-25.2] Months, CCB: 32.9 [95% CI, 22.5-43.3] Months, Log Rank *P* = .158)**



Abbreviations: ACE = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; ASI = angiotensin system inhibitors; BB = beta blockers; CCB = calcium channel blocker; CI = confidence interval; cPFS = progression based on radiologic or clinical evidence.

Supplemental Table 1 Demographics of mRCC Patients Treated With Sunitinib During Observation Period

Characteristic	All Patients	Eligible Patients	Ineligible Patients	*P*
No. of patients	146 (100%)	72 (49.3%)	74 (50.7%)	
Gender				.88
Male	103 (70.5)	49 (68)	54 (73)	
Age at diagnosis of RCC, years	61 (27-84)	62.0 (27-82)	60 (38-80)	.16
Nephrectomy	134 (91.7)	67 (93)	67 (90.5)	.6
Histology				.37
Clear-cell histology	117 (80.1)	58 (80.6)	59 (79.7)	
Grade				.6
≤2	86 (59)	47 (65.3)	39 (52.7)	
≥3	38 (26)	16 (22.2)	22 (29.7)	
NE	22 (15)	9 (12.5)	13 (17.6)	
T Stage at RCC Diagnosis				
≤2	42 (28.8)	22 (30.5)	20 (27)	
≥3	82 (56.1)	41 (55.6)	41 (55.6)	
NE	22 (15.1)	9 (12.5)	13 (17.6)	
Synchronous metastasis	39 (26.7)	21 (29.2)	18 (24.3)	.98
Time from RCC diagnosis to mRCC onset, months	7 (0-203)	7 (0-203)	6.5 (0-198)	.58
No. of metastatic organ sites	2 (1-8)	2 (1-8)	2 (1-4)	.18
ECOG PS at mRCC Onset				.91
0	102 (69.8)	62 (86.1)	40 (54.1)	
1	12 (8.2)	8 (11.1)	4 (5.4)	
2	3 (2.1)	2 (2.8)	1 (1.3)	
NE	29 (19.9)	0 (0)	29 (39.2)	
Time from diagnosis of RCC to first-line treatment, months	15 (0-343)	17 (0-187)	13.5 (0-343)	.83
Age at start of sunitinib treatment, years	61.8 (37.7-84.5)	62.5 (39-82)	61.3 (37.7-84.5)	.9
No. of therapy line of sunitinib administration	1 (1-6)	2 (1-6)	1 (1-4)	.2
Sunitinib treatment duration, months	7 (0.4-32.7)	8.43 (0.5-33.13)	6.2 (0.4-30)	.4
cPFS, months, median (95% CI)	8 (5.9-10)	8.3 (4.7-12)	7 (3.8-10.2)	.084
OS, months, median (95% CI)	28.4 (23.7 -33.1)	23.6 (14.7-32.4)	30 (23.7-36.3)	.003

Observation period was June 2004 to February 2011. Data are presented as n (%) or median (range) unless otherwise indicated.
Abbreviations: CI = confidence interval; cPFS = progression based on radiologic or clinical evidence; ECOG PS = Eastern Cooperative Oncology Group performance status; mRCC = metastatic renal-cell carcinoma; NE = not evaluable; OS = overall survival; RCC = renal-cell carcinoma.

Supplemental Table 2 Risk Factor–Adjusted Multivariate Binary Logistical Regression for Treatment-Related HTN

Parameter	*P*	OR (95% CI)
Adjustment: Gender		
Age >50 years	.016	5.97 (1.4-25.38)
Starting dose sunitinib 50 mg	.02	8.48 (1.41-50.97)
Pre-HTN[a]	.038	4.84 (1.09-21.42)
Gender	.643	1.37 (0.37-5.1)
Adjustment: Diabetes		
Age >50 years	.015	5.87 (1.42-24.28)
Starting dose sunitinib 50 mg	.017	9.15 (1.48-56.67)
Pre-HTN[a]	.037	4.81 (1.1-21.1)
Diabetes	.354	0.5 (0.11-2.19)
Adjustment: Smoking[a]		
Age >50 years	.023	5.3 (1.26-22.22)
Starting dose sunitinib 50 mg	.018	8.85 (1.45-53.95)
Pre-HTN[a]	.031	5.09 (1.16-22.27)
Smoking[a]	.781	0.79 (0.15-4.12)
Adjustment: Alteration of Lipid Metabolism[a]		
Age >50 years	.016	5.57 (1.37-22.57)
Starting dose sunitinib 50 mg	.017	8.97 (1.49-54.21)
Pre-HTN[a]	.024	6.1 (1.27-29.3)
Alteration of lipid metabolism[a]	.175	0.33 (0.06-1.65)

Abbreviations: CI = confidence interval; HTN = hypertension; OR = odds ratio.
[a]Definition provided in Patients and Methods.