Original Study

Angiotensin Inhibitors as Treatment of Sunitinib/Pazopanib-induced Hypertension in Metastatic Renal Cell Carcinoma

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Abstract

Previous preclinical research suggests that angiotensin system inhibitors may have a direct anti-angiogenic effect that may be synergistic with the currently available angiogenesis inhibitors. In this retrospective study, we reviewed 303 patients with metastatic renal cell carcinoma treated with first-line angiogenesis inhibitors. Our results demonstrate a longer overall and progression-free survival for angiotensin system inhibitor users among patients with treatment-related hypertension. If validated, these results may guide the choice of antihypertensive medication among patients being treated with angiogenesis inhibitors.

Background: Research suggests that baseline use of angiotensin system inhibitors (ASIs) improves outcome in patients with metastatic renal cell carcinoma (mRCC), but it remains unknown whether the type of antihypertensive medication used to initiate management at onset of treatment-induced hypertension (HTN) is associated with outcome. We evaluated the association of ASIs and outcome among patients with mRCC treated with first-line tyrosine kinase inhibitors (TKIs). **Patients and Methods:** We identified 303 consecutive patients with mRCC who were treated with sunitinib or pazopanib in a single university hospital cancer center. Statistical analyses were performed using the Kaplan-Meier method and Cox regression adjusted for known risk factors. **Results:** Progression-free survival (PFS) and overall survival (OS) were similar among patients with baseline HTN (n = 197; 65%) versus patients with no baseline HTN (n = 106; 35%) (PFS; $P = .72$) (OS; $P = .54$). There was a significant difference between patients with treatment-induced HTN (n = 110) versus patients with no treatment-induced HTN (n = 193) for PFS (15.6 vs. 6.4 months, respectively; $P < .001$) and OS (34.9 vs. 13.9 months, respectively; $P < .001$). Use of ASIs at baseline (n = 126; 41.6%) had no impact on outcome as compared with patients receiving other antihypertensive medication (n = 71; 23.4%) or with patients with no baseline antihypertensive medication (n = 106; 35.0%). Among patients with TKI-induced HTN (n = 110), however, ASI users (n = 91) demonstrated improved OS (37.5 vs. 18.1 months; $P = .001$) and PFS (17.1 vs. 7.2 months; $P = .004$) versus ASI nonusers (n = 19), respectively. **Conclusion:** Our results demonstrate survival benefit for ASI users among patients with TKI-induced HTN. These results, however, require further validation in a prospective setting.

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Introduction

Hypertension (HTN) is a well-known side effect associated with anti-vascular endothelial growth factor (VEGF) therapies in metastatic renal cell carcinoma (mRCC), and numerous studies have reported it as predictive of better outcome for patients treated with tyrosine kinase inhibitors (TKIs).[1-5]

The pathogenesis of treatment-related HTN is likely multifactorial. Evidence suggests that inhibition of VEGF leads to impairment of vasodilatory mechanisms, thus increasing the resistance of peripheral blood vessels.[6,7] Structural or functional vascular rarefaction caused by antiangiogenic agents,[8] as well as decreased glomerular filtration rate and increased sodium and water retention by the kidney, owing to placenta-derived soluble antiangiogenic factors,[9] may also play a role in the development of therapy-related HTN.

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HTN may also contribute to the development of RCC based on its significantly higher incidence among patients with mRCC.[4,10,11] A recent study consisting of patients treated with sunitinib, a standard first-line treatment, suggested that baseline HTN might be associated with better outcome.[12]

Angiotensin system inhibitors (ASIs), which are commonly used as antihypertensive agents, have been of great interest in treatment of mRCC-related HTN. Xenograft studies have demonstrated that angiotensin II receptor-deficient mice have reduced angiogenesis and tumor growth rates compared with wild-type mice,[13] and preclinical studies have shown that ASIs possess antiangiogenic potential.[14-16]

In 2010 Dolley-Hitze et al[17] demonstrated that overexpression of angiotensin II receptors (AT1-R and AT2-R) in mRCC correlates with more aggressive tumor behavior and shorter progression-free survival (PFS). Keizman et al[18] were the first to illustrate that baseline use of ASIs may improve PFS in sunitinib-treated patients with mRCC. More recently, in a large pooled retrospective analysis, McKay et al[19] confirmed that ASI users may have an improved survival over ASI nonusers. However, it remains unclear whether choosing ASIs as treatment at onset of therapy-related HTN has beneficial effect on outcome among patients with mRCC.

The aim of this study was to examine the potential impact of the use of ASIs on outcome among a large cohort of patients with mRCC treated with first-line TKIs, and to investigate whether the selection of ASIs as anti-HTN agents improve outcome of patients with mRCC as compared with patients treated with other anti-HTN agents (such as β-blockers/Ca-blockers/diuretics).

Patients and Methods

Patients and Treatment

A total of 303 consecutive patients with mRCC were treated with a first-line anti-VEGF agent, of which 267 patients were treated with sunitinib and 36 with pazopanib at the Cancer Center, Helsinki University Central Hospital, between October 18, 2006 and December 31, 2014. The data collected from the hospital case records included patient demographic features, treatments given, adverse events (AEs), hospitalizations, and outcome data.

None of the patients had received prior TKI therapy. Twenty-two (7.3%) patients had received prior interferon alfa. Both sunitinib and pazopanib were administered according to standard care until disease progression or unacceptable toxicity. Twenty-three percent (n = 59) of the patients started sunitinib with intermittent dosing (4 weeks on-treatment, 2 weeks off-treatment) and 77% (n = 208) with continuous dosing. Pazopanib was administered continuously.

Assessment of Tumor Response and AEs

Response to treatment was assessed by physical examination and computed tomography at 8 to 12 week intervals. Treatment efficacy was reported according to Response Evaluation Criteria in Solid Tumours v. 1.0 (RECIST).[20] AEs were captured every 4 to 6 weeks and were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.[21] HTN was graded as follows: Grade 1, transient (< 24 hours), asymptomatic, blood pressure (BP) rise by 20 mmHg (diastolic) or to > 150 mmHg, if previously normal; Grade 2, recurrent, persistent, or symptomatic rise in diastolic BP > 20 mmHg or systolic BP rise to > 150/100 mmHg, if previously normal (monotherapy with antihypertensive agents may be indicated); Grade 3, requiring more than 1 drug or more intensive therapy than previously.

Assessment of BP and Use of Antihypertensive Agents

BP was assessed at baseline and at the end of each treatment cycle. The patients were additionally instructed to measure their BP on a daily basis and to contact their physician for systolic BP > 150 mmHg or diastolic BP > 90 mmHg. Baseline HTN was defined based on International Classification of Diseases, Tenth Revision (ICD-10) diagnosis code for HTN in the patient case records or as the use of 1 or more antihypertensive agents prior to treatment initiation. Treatment-induced HTN was defined as recurrent, persistent, or symptomatic rise in diastolic BP of > 20 mmHg or systolic BP rise to > 150 mmHg, if previously within normal range (CTCAE, grade ≥ 2). These data were captured from patient case records. The use of antihypertensive medication was obtained from the patient case records before treatment initiation and during follow-up. ASIs included angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers. The baseline use of ASIs and other antihypertensive agents was defined as patients receiving ASIs or other antihypertensive agents prior to treatment initiation. The initiation of ASIs and other antihypertensive agents, as well as dose escalations, as treatment of TKI-induced HTN was considered to have occurred when it was documented on patient case records.

Statistics

In this retrospective study, the patients' characteristics were described overall and by HTN and ASI user status at baseline. The groups were compared using the Mann-Whitney *U* test for continuous data and the χ^2 test for categorical data. The 2 endpoints in the study were (1) overall survival (OS), defined as the time from treatment initiation to death, whatever the cause; and (2) PFS, defined as the time from treatment initiation to the first event (tumor progression or death from any cause). The Kaplan-Meyer method was used to estimate the median survival times with 95% confidence intervals (CIs) for both OS and PFS, censoring the patients who were alive or had no disease progression at the last follow-up visit. The univariate Cox proportional hazards models were used to compare the survival times between groups that were defined according to the HTN and ASI user status. In addition, the multivariate Cox proportional hazard models were performed, and the additional predictors were: number of metastatic sites, prior nephrectomy, Heng risk criteria (Karnofsky performance status less than 80%; diagnosis-to-treatment interval less than 1 year; and abnormal levels of hemoglobin, platelets, neutrophils, or calcium),[22] and treatment-induced HTN. The results are given as nonadjusted or adjusted hazard ratios (HRs) with 95% CIs. Subgroup analysis was performed on patients developing treatment-associated HTN.

Because treatment-associated HTN, and therefore the use of ASIs and other antihypertensive medication, is a time-dependent covariate, a landmark survival analysis with the landmark set at 3 months after date of initiation of anti-VEGF therapy was applied to avoid bias from longer treatment. According to the landmark method, patients with short treatment (ie, less than 3 months) were excluded.

PFS and OS landmark analyses included those patients who were alive and had no disease progression before the landmark time point. In the landmark analysis, OS and PFS were defined as the time from the landmark to progression or death from any cause.

Statistical tests were 2-sided, and *P*-values < .05 were considered as statistically significant. Analysis was performed using IBM SPSS Statistics for Windows (version 23.0; IBM Corp, Armonk, NY).

Results

Patient Characteristics

The study population consisted of 303 patients. Patient characteristics are shown in Supplemental Table 1 (in the online version). The median age was 67 years (range, 22-92 years), and the median follow-up time of patients alive was 53.3 months. Most patients had undergone prior nephrectomy (79.5%), and the majority had RCC with a clear-cell histology (87.2%). Out of the 303 patients, 181 (59.7%) stopped treatment owing to progression, and 95 (31.4%) were without progression (80 for AEs, 15 for other reasons). The remaining 27 patients (8.9%) continued treatment at the time of data cutoff. OS and PFS for the study population were 20.3 months (95% CI, 17.0-23.6 months) and 8.2 months (95% CI, 6.9-9.6 months), respectively. Of the evaluable patients, 5 (1.8%) had complete response, 83 (29.7%) had partial response, 134 (48.0%) had stable disease, and 57 (20.4%) had progressive disease as their best response.

Effect of HTN and ASIs on Outcome

A total of 197 (65%) patients had baseline HTN. Of these, 126 (64%) patients had ASI (angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker) as baseline antihypertensive medication either as monotherapy or in combination with other approved antihypertensive medication.

Patients with HTN and patients with ASI were significantly older compared with patients without HTN and without ASI. There were no statistically significant differences in other patient characteristics. In univariate analysis, there was no significant difference in outcome for patients with baseline HTN versus no HTN at baseline in OS (20.3 months [95% CI, 16.4-24.2 months] vs. 20.1 months [95% CI, 15.5-24.7 months]; respectively) or PFS (8.2 months [95% CI, 6.6-9.7 months] vs. 8.2 months [95% CI, 5.4-11.0 months]; $P = .54$ and $P = .72$, respectively). When comparing patients receiving ASIs at baseline (n = 126) with patients receiving other antihypertensive medication (n = 71) or with patients with no antihypertensive medication at baseline (n = 106), there was no significant difference in outcome for OS (22.3 months [95% CI, 18.9-25.7 months] vs. 16.5 months [95% CI, 10.8-22.2 months] vs. 20.1 months [95% CI, 15.5-24.7 months]; respectively, with global $P = .35$) or PFS (8.6 months [95% CI, 6.3-10.9 months] vs. 7.3 months [95% CI, 5.0-9.6 months] vs. 8.2 months [95% CI, 5.4-11.0 months]; respectively, with global $P = .63$).

Patients with treatment-induced HTN (n = 110) had significantly longer OS (34.9 months [95% CI, 28.2-41.6 months] vs. 13.9 months [95% CI, 10.4-17.4 months], respectively; unadjusted HR, 0.41; 95% CI, 0.30-0.55; $P < .001$) and PFS (15.6 months [95% CI, 11.6-19.7 months] vs. 6.4 months [95% CI, 5.6-7.3 months], respectively; unadjusted HR, 0.43; 95% CI, 0.33-0.56; $P < .001$) when compared with patients who did not develop HTN

Table 1 HTN and Use of ASI at Baseline and During Treatment in Association With OS and PFS Among Patients With mRCC

Predictor	Baseline Status	During Treatment	N	OS			PFS		
				Median (95% CI)	HR (95% CI)	*P*	Median (95% CI)	HR (95% CI)	*P*
HTN	No	HTN did not develop	71	14.2 (8.5-19.9)	1.00		6.5 (5.4-7.7)	1.00	
	No	HTN developed	35	44.1 (26.0-62.2)	0.31 (0.17-0.54)	<.001	17.6 (5.4-29.8)	0.32 (0.19-0.52)	<.001
	Yes	HTN did not worsen	122	13.2 (8.1-18.3)	1.03 (0.75-1.43)	.85	6.0 (4.7-7.3)	0.96 (0.71-1.30)	.79
	Yes	HTN did worsen	75	33.7 (20.6-46.8)	0.47 (0.32-0.69)	<.001	15.1 (10.4-19.9)	0.47 (0.33-0.67)	<.001
ASI use	No	ASI was not started	138	16.0 (12.1-19.9)	1.00		6.5 (5.5-7.5)	1.00	
	No	ASI was started	39	58.7 (38.0-79.5)	0.27 (0.16-0.46)	<.001	24.7 (13.2-36.2)	0.31 (0.20-0.48)	<.001
	Yes	Dose was not increased	94	18.6 (12.2-25.0)	0.81 (0.60-1.09)	.17	7.0 (4.9-9.1)	0.81 (0.61-1.07)	.14
	Yes	Dose was increased	32	34.9 (28.7-41.1)	0.45 (0.28-0.72)	.001	14.2 (6.7-21.8)	0.47 (0.31-0.74)	.001

Abbreviations: ASI = angiotensin system inhibitors; CI = confidence interval; HR = hazard ratio; HTN = hypertension; mRCC = metastatic renal cell carcinoma; OS = overall survival; PFS = progression-free survival.

during therapy. For patients receiving ASI either as a new drug (n = 39) or having ASI dose intensified (n = 32) during TKI treatment (total n = 71), there was a significant difference for both OS (37.7 months [95% CI, 26.0-49.5 months] vs. 16.5 months [95% CI, 12.9-20.2 months], respectively; unadjusted HR, 0.38; 95% CI, 0.26-0.54; $P < .001$) and PFS (16.7 months [95% CI, 6.1-27.2 months] vs. 6.6 months [95% CI, 5.8-7.5 months], respectively; unadjusted HR, 0.41; 95% CI, 0.30-0.57; $P < .001$), when compared with patients who did not receive ASIs as new anti-HTN medication or have their pre-existing ASI dose escalated (n = 232). Factors associated with OS and PFS in univariate analysis are shown in Supplemental Table 2 (in the online version).

To analyze the impact of HTN and ASI use in detail, we divided all patients into 4 groups according to HTN and ASI user status (Table 1). The outcome for both OS and PFS was best among patients who developed HTN during treatment or started ASI as a new anti-HTN medication during treatment.

To further examine the effects of ASI use on outcome, we divided the patients with TKI-induced HTN (n = 110) into 4 groups according to baseline ASI use and ASI-initiation/dose-escalation during treatment (Table 2). With ASI nonusers as the reference group, this subgroup analysis suggests that both OS and PFS are longest among patients who started using ASI as a novel treatment for TKI-induced HTN (OS; $P < .001$) (PFS; $P = .001$). Patients who used ASIs at baseline and either had their ASI dose intensified or received other antihypertensive medication as treatment of TKI-induced HTN also had both longer OS ($P = .01$ and $P = .02$, respectively) and PFS ($P = .048$ and $P = .06$, respectively) when compared with the reference group. Among patients with TKI-induced HTN, ASI users (ASI during baseline and/or during treatment; n = 91) had significantly longer OS of 37.5 months (95% CI, 28.2-46.8 months) versus 18.1 months (95% CI, 14.0-22.2 months; $P = .001$) and PFS of 17.1 months (95% CI, 9.3-24.9 months) versus 7.2 months (95% CI, 3.7-10.7 months; $P = .004$) as compared with ASI nonusers (n = 19). These groups were balanced regarding relevant clinicopathologic covariables. Patient characteristics are shown in Supplemental Table 3 (in the online version). A pooled survival analysis of all ASI users versus ASI nonusers among patients with TKI-induced HTN is depicted in Figure 1A and B.

Multivariate Survival Analysis

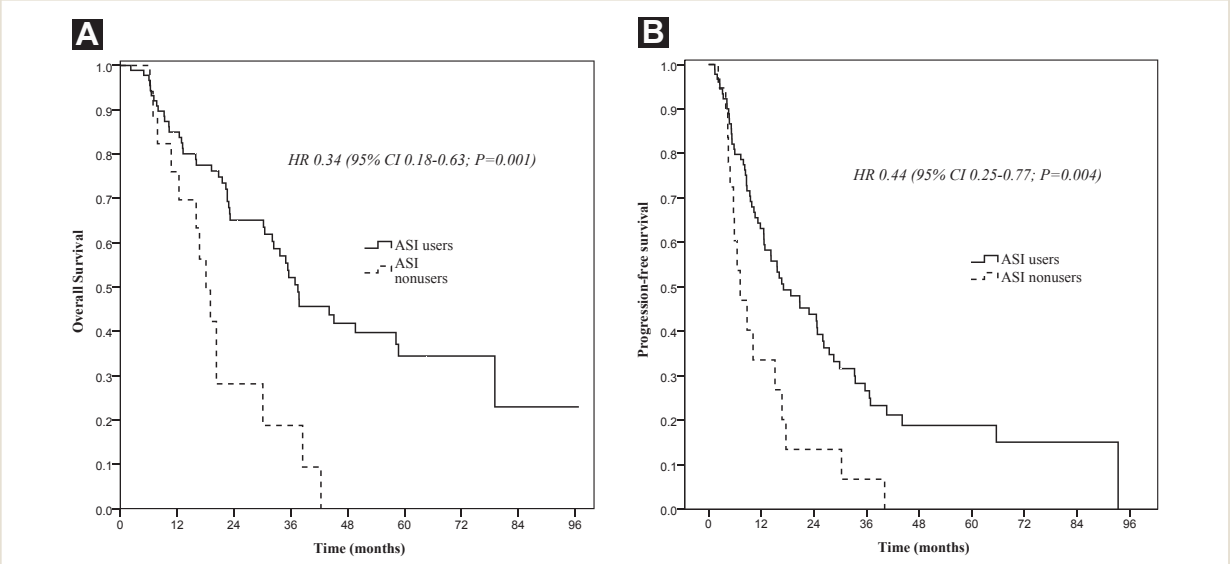
To investigate the independent impact of different factors on outcome, we performed a multivariate survival analysis adjusted for number of metastatic sites, prior nephrectomy, Heng criteria, and treatment-induced HTN. Because neither HTN nor ASI use at baseline had a statistically significant impact on outcome in the univariate analysis, they were excluded from the multivariate analysis. Owing to the strong positive correlation between treatment-induced HTN and ASI use during treatment (Cramer's phi = 0.73), only HTN was entered in the analysis. In the multivariate analysis, treatment-induced HTN was statistically associated with both longer OS (adjusted HR, 0.49; 95% CI, 0.35-0.67; $P < .001$) and PFS (adjusted HR, 0.50; 95% CI, 0.38-0.67; $P < .001$). We additionally performed a multivariate analysis among patients with TKI-induced HTN. The final model was adjusted for Heng risk criteria and ASI user status. In this analysis,

Table 2 Use of ASI at Baseline and During Treatment in Association with OS and PFS Among Patients With mRCC With Treatment-induced HTN (n = 110)

Use of ASI at Baseline	Use of ASI During Treatment	N	OS			PFS		
			Median (95% CI)	HR (95% CI)	*P*	Median (95% CI)	HR (95% CI)	*P*
No	ASI was not started	19	18.1 (14.0-22.2)	1.00		7.2 (3.7-10.7)	1.00	
No	ASI was started	39	58.7 (38.0-79.5)	0.26 (0.12-0.55)	<.001	24.7 (13.2-36.2)	0.35 (0.18-0.67)	.001
Yes	Dose was not increased	20	35.6 (15.4-55.7)	0.35 (0.15-0.81)	.01	17.1 (11.4-22.8)	0.49 (0.24-0.99)	.048
Yes	Dose was increased	32	34.9 (28.7-41.1)	0.43 (0.21-0.87)	.02	14.2 (6.7-21.8)	0.54 (0.28-1.02)	.06

Abbreviations: ASI = angiotensin system inhibitors; CI = confidence interval; HR = hazard ratio; HTN = hypertension; mRCC = metastatic renal cell carcinoma; OS = overall survival; PFS = progression-free survival.

Figure 1 Kaplan-Meier Survival Curves for Overall Survival (A) and Progression-free Survival (B) in Patients With mRCC With TKI-induced Hypertension (n = 110). The Cox Proportional Hazard Model Was Used to Compare the ASI Users (ASI During Baseline and/or During Treatment, n = 91) With the ASI Nonusers (n = 19)



Abbreviations: ASI = angiotensin system inhibitors; CI = confidence interval; HR = hazard ratio; mRCC = metastatic renal cell carcinoma; TKI = tyrosine kinase inhibitors.

the use of ASIs had an independent protector effect for OS (adjusted HR, 0.35; 95% CI, 0.18-0.66; $P = .001$) and PFS (adjusted HR, 0.42; 95% CI, 0.23-0.77; $P = .005$).

Landmark Analysis

To verify whether the early incidence of treatment-induced HTN and ASI use was truly predictive, we performed a 3-month landmark analysis. For this purpose, each patient's HTN status, as well as use of ASIs, was determined within the landmark time point. In this analysis, patients with treatment-induced HTN (n = 81) had significantly longer OS (34.5 months [95% CI, 30.5-38.5 months] vs. 17.1 months [95% CI, 14.3-19.9 months]; $P < .001$) and PFS (13.7 months [95% CI, 7.5-19.9 months] vs. 4.9 months [95% CI, 3.8-6.1]; $P < .001$) than patients with no development of HTN (n = 172). Similar to the results of the primary analysis, among patients with TKI-induced HTN, ASI users (n = 68) had significantly longer OS (42.1 months [95% CI, 17.4-66.8 months] vs. 17.3 months [95% CI, 13.9-20.7 months]; $P = .004$) and PFS (15.7 months [95% CI, 7.6-23.8 months] vs. 5.8 months [95% CI, 0.3-11.2 months]; $P = .011$) as compared with ASI nonusers (n = 13).

Discussion

Our present study suggests that patients treated with anti-VEGF agents may benefit from ASI use as treatment of TKI-induced hypertension. As depicted in Table 2, patients receiving ASI as novel anti-HTN medication for treatment-induced HTN had the longest OS and PFS. Furthermore, we demonstrate that OS and PFS were significantly longer among patients with treatment-related HTN for ASI users versus ASI nonusers (Figure 1A and B). These differences remained significant in a 3-month landmark analysis and in a multivariate model adjusted for Heng risk criteria and ASI user status.

Since Keizman et al[18] first demonstrated a significant 7-month increase of PFS (HR, 0.54; $P = .02$) in favor of ASI users in mRCC, a few studies have examined the impact of ASI use on outcome among patients with mRCC. Recently, Izzedine et al[12] demonstrated a survival benefit for patients receiving ASI before or within 1 cycle of sunitinib treatment (OS; HR, 0.40; 95% CI, 0.24-0.66; $P < .001$ and PFS; HR, 0.55; 95% CI, 0.35-0.86; $P = .009$). Similar results were reported by McKay et al[19] in a large retrospective analysis. To the best of our knowledge, however, there are no reports on whether the selection of ASIs as treatment at onset of TKI-induced HTN affects outcome.

Considering the growing evidence implicating the angiotensin system as a potential factor in the tumorigenesis process, it remains unclear why no statistically significant difference in outcome for baseline ASI users versus ASI nonusers was seen. We hypothesize that the rather small number of patients in our patient cohort might fail to recognize the differences as statistically significant. Additionally, our patient cohort differs somewhat from those used by McKay et el and Keizman et al regarding prior systemic therapy, incidence of treatment-associated HTN, and OS for the whole patient cohort.[18,19] Lastly, in these studies, ASI use was determined as ASI use at baseline or within 1 month of therapy, which might reflect and correlate to some extent with the onset of TKI-induced hypertension − a well-known predictor of anti-VEGF treatment efficacy.

Our data suggests that patients who benefit from anti-VEGF treatment the most also benefit the most from ASI, given that

statistically significant differences were not seen in outcomes between ASI users and ASI nonusers among patients who did not develop TKI-induced HTN in contrast to patients who did develop HTN during treatment. We hypothesize that this might represent a synergistic effect between anti-VEGF agents and ASIs, because there is evidence showing that angiotensin II plays a role in VEGF-dependent angiogenesis.[23,24] Miyajima et al[25] reported that candesartan alone dramatically prevents development of metastatic lung nodules along with the inhibition of neovascularization and VEGF-expression in a murine RCC model. More recently, in another murine RCC model, telmisartan was shown to potentiate the antiangiogenic effects of sunitinib.[26] Preclinical data suggest ASIs to have anti-tumor and antiangiogenic potential in other cancer types as well.[27,28]

Several studies have reported TKI-induced HTN as a predictor of treatment efficacy.[2-5,12,19] In our analysis, we were able to confirm these findings with TKI-induced HTN having an independent effect on outcome (HR, 0.49; 95% CI, 0.35-0.67; $P < .001$ and HR, 0.50; 95% CI, 0.38-0.67; $P < .001$) for OS and PFS, respectively. There was no correlation between baseline HTN and outcome; a result in line with earlier findings.[19]

Although the present series was retrospective in nature, it was based on consecutive patients. There are some limitations to our study, however. Our study population represents a heterogeneous group of patients including different histologic variants of RCC treated with either sunitinib or pazopanib. No conclusions regarding other anti-VEGF agents can be drawn. Data were lacking regarding the precise dosing, schedule, and possible discontinuations of ASI use, and we assumed on-label usage of these agents. Additionally, data were lacking regarding why some patients were treated with ASIs and some not. This uncertainty related to ASI selection criteria might represent possible confounding factors (eg, renal dysfunction that were not adjusted for in the analysis). In statistical analysis, ASI use could not be verified as an independent predictor of better outcome in a multivariable model for the entire cohort owing to the strong correlation of treatment-induced HTN and ASI use. Furthermore, the total number of 19 ASI nonusers in the subgroup of patients with TKI-induced HTN is relatively small.

Conclusions

We conclude that the present data demonstrate both a prolonged OS and PFS for ASI users over ASI nonusers among patients with treatment-related HTN in a large cohort of patients with mRCC. In recognition of the limitations of the present series and the fact that ASI use could not be verified as an independent predictor of outcome for the entire cohort due to strong correlation of ASI use and TKI-induced HTN, further studies investigating ASIs in this setting are warranted to confirm our findings. However, should these results be validated in a prospective setting, in the absence of contraindications, selecting ASIs as a first anti-HTN agent might offer a survival benefit as well as feasible management of TKI-induced HTN in patients with mRCC.

Clinical Practice Points

- HTN is a class effect of anti-VEGF agents used in the treatment of mRCC.
- Preclinical studies suggest that ASIs may have direct anti-angiogenic effects, which may be synergistic with the currently available angiogenesis inhibitors.
- Angiotensin inhibitors are widely used in the treatment of HTN. It remains unclear, however, whether choosing ASIs as treatment of therapy-related HTN has beneficial effect on outcome among patients with mRCC.
- We analyzed anti-HTN treatment among 303 consecutive patients with mRCC treated with first-line TKIs.
- In this study, we demonstrate a longer OS (adjusted HR, 0.35; 95% CI, 0.18-0.66; $P = .001$) and PFS (adjusted HR, 0.42; 95% CI, 0.23-0.77; $P = .005$) for ASI users among patients with TKI-induced HTN.
- If validated, these results may guide the choice of antihypertensive medication among patients being treated with angiogenesis inhibitors.

Disclosure

P. Penttilä has received honoraria from Novartis. K. Peltola has received honoraria from Novartis, BMS, Pfizer, Amgen, Astellas, Sanofi, Merck, and Eli Lilly. P. Bono has received research funding from Novartis and honoraria from Pfizer, Novartis, Orion Pharma, BMS, and MSD. All other authors state that they have no conflicts of interest.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clgc.2016.12.016.

References

1. Rixe O, Billemont B, Izzedine H. Hypertension as a predictive factor of sunitinib activity. *Ann Oncol* 2007; 18:1117.
2. Rini BI, Cohen DP, Lu DR, et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst* 2011; 103:763-73.
3. Rini BI, Schiller JH, Fruehauf JP, et al. Diastolic blood pressure as a biomarker of axitinib efficacy in solid tumors. *Clin Cancer Res* 2011; 17:3841-9.
4. Li Y, Li S, Zhu Y, et al. Incidence and risk of sorafenib-induced hypertension: a systematic review and meta-analysis. *J Clin Hypertens (Greenwich)* 2014; 16:177-85.
5. Bono P, Rautiola J, Utriainen T, Joensuu H. Hypertension as predictor of sunitinib treatment outcome in metastatic renal cell carcinoma. *Acta Oncol* 2011; 50:569-73.
6. Wei W, Jin H, Chen ZW, Zioncheck TF, Yim AP, He GW. Vascular endothelial growth factor-induced nitric oxide- and PGI2-dependent relaxation in human internal mammary arteries: a comparative study with KDR and Flt-1 selective mutants. *J Cardiovasc Pharmacol* 2004; 44:615-21.
7. Yang R, Thomas GR, Bunting S, et al. Effects of vascular endothelial growth factor on hemodynamics and cardiac performance. *J Cardiovasc Pharmacol* 1996; 27:838-44.
8. Steeghs N, Gelderblom H, Roodt JO, et al. Hypertension and rarefaction during treatment with telatinib, a small molecule angiogenesis inhibitor. *Clin Cancer Res* 2008; 14:3470-6.
9. Dechend R, Luft FC. Angiogenesis factors and preeclampsia. *Nat Med* 2008; 14: 1187-8.
10. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. *Nat Rev Urol* 2010; 7:245-57.
11. Haggstrom C, Rapp K, Stocks T, et al. Metabolic factors associated with risk of renal cell carcinoma. *PLoS One* 2013; 8:e57475.
12. Izzedine H, Derosa L, Le Teuff G, Albiges L, Escudier B. Hypertension and angiotensin system inhibitors: impact on outcome in sunitinib-treated patients for metastatic renal cell carcinoma. *Ann Oncol* 2015; 26:1128-33.
13. Egami K, Murohara T, Shimada T, et al. Role of host angiotensin II type 1 receptor in tumor angiogenesis and growth. *J Clin Invest* 2003; 112:67-75.
14. Noguchi R, Yoshiji H, Ikenaka Y, et al. Synergistic inhibitory effect of gemcitabine and angiotensin type-1 receptor blocker, losartan, on murine pancreatic tumor growth via anti-angiogenic activities. *Oncol Rep* 2009; 22:355-60.
15. Noguchi R, Yoshiji H, Kuriyama S, et al. Combination of interferon-beta and the angiotensin-converting enzyme inhibitor, perindopril, attenuates murine hepatocellular carcinoma development and angiogenesis. *Clin Cancer Res* 2003; 9: 6038-45.

16. Yoshiji H, Kuriyama S, Noguchi R, Fukui H. Angiotensin-I converting enzyme inhibitors as potential anti-angiogenic agents for cancer therapy. *Curr Cancer Drug Targets* 2004; 4:555-67.
17. Dolley-Hitze T, Jouan F, Martin B, et al. Angiotensin-2 receptors (AT1-R and AT2-R), new prognostic factors for renal clear-cell carcinoma? *Br J Cancer* 2010; 103:1698-705.
18. Keizman D, Huang P, Eisenberger MA, et al. Angiotensin system inhibitors and outcome of sunitinib treatment in patients with metastatic renal cell carcinoma: a retrospective examination. *Eur J Cancer* 2011; 47:1955-61.
19. McKay RR, Rodriguez GE, Lin X, et al. Angiotensin system inhibitors and survival outcomes in patients with metastatic renal cell carcinoma. *Clin Cancer Res* 2015; 21:2471-9.
20. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92:205-16.
21. Trotti A, Colevas A, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003; 13:176-81.
22. Heng DYC, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor–targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009; 27:5794-9.
23. Deshayes F, Nahmias C. Angiotensin receptors: a new role in cancer? *Trends Endocrinol Metabol* 2005; 16:293-9.
24. Rosenthal T, Gavras I. Angiotensin inhibition and malignancies: a review. *J Hum Hypertens* 2009; 23:623-35.
25. Miyajima A, Kosaka T, Asano T, et al. Angiotensin II type I antagonist prevents pulmonary metastasis of murine renal cancer by inhibiting tumor angiogenesis. *Cancer Res* 2002; 62:4176-9.
26. Verhoest G, Dolley-Hitze T, Jouan F, et al. Sunitinib combined with angiotensin-2 type-1 receptor antagonists induces more necrosis: a murine xenograft model of renal cell carcinoma. *Biomed Res Int* 2014; 2014:901371.
27. Arafat HA, Gong Q, Chipitsyna G, Rizvi A, Saa CT, Yeo CJ. Antihypertensives as novel antineoplastics: angiotensin-I-converting enzyme inhibitors and angiotensin II type 1 receptor blockers in pancreatic ductal adenocarcinoma. *J Am Coll Surg* 2007; 204:996-1005, discussion: 1005-6.
28. Yoshiji H, Noguchi R, Ikenaka Y, Kaji K, Aihara Y, Fukui H. Impact of renin-angiotensin system in hepatocellular carcinoma. *Curr Cancer Drug Targets* 2011; 11:431-41.

Supplemental Table 1 Patient Characteristics by HTN and ASI User Status at Baseline

	HTN at Baseline			ASI as anti-HTN Medication at Baseline			
	Yes N (%)	No N (%)	*P*	Yes N (%)	No N (%)	*P*	Total N (%)
Total	197	106		126	177		303
Gender							
Male	127 (64.5)	66 (62.3)	.71	83 (65.9)	110 (62.1)	.55	193 (63.7)
Female	70 (35.5)	40 (37.7)		43 (34.1)	67 (37.9)		110 (36.3)
Age[a]							
Median	67	64	.015	67	66	.04	67
Range	39-92	22-82		39-89	22-92		22-92
WHO							
0-1	161 (81.7)	83 (78.3)	.54	104 (82.5)	140 (79.1)	.56	244 (80.5)
>1	36 (18.3)	23 (21.7)		22 (17.5)	37 (20.9)		59 (19.5)
Prior nephrectomy							
Yes	159 (80.7)	82 (77.4)	.55	105 (83.3)	136 (76.8)	.19	241 (79.5)
No	38 (19.3)	24 (22.6)		21 (16.7)	41 (23.2)		62 (20.5)
Histology							
Clear-cell	142 (89.3)	70 (83.3)	.23	94 (91.3)	118 (84.3)	.12	212 (87.2)
Non—clear-cell	17 (10.7)	14 (16.7)		9 (8.7)	22 (15.7)		31 (12.8)
Missing	38	22		23	37		60
No. of metastatic sites							
0-1	56 (28.4)	28 (26.4)	.79	32 (25.4)	52 (29.4)	.52	84 (27.7)
>1	141 (71.6)	78 (73.6)		94 (74.6)	125 (70.6)		219 (72.3)
Heng criteria							
Favorable	30 (16.2)	19 (18.3)	.52	25 (21.0)	24 (14.1)	.21	49 (17.0)
Intermediate	97 (52.4)	42 (40.4)	.05	59 (49.6)	80 (47.0)	.72	139 (48.1)
Poor	58 (31.4)	43 (41.3)	.13	35 (29.4)	66 (38.8)	.13	101 (34.9)
Missing	12	2		7	7		14
Treatment							
Sunitinib	171 (86.8)	96 (90.6)	.36	106 (84.1)	161 (91.0)	.075	267 (88.1)
Pazopanib	26 (13.2)	10 (9.4)		20 (15.9)	16 (9.0)		36 (11.9)

Abbreviations: ASI = angiotensin system inhibitors; HTN = hypertension; WHO = World Health Organization.
[a]Patients with HTN and with ASI were significantly older compared with patients without HTN and ASI, respectively. Other patient characteristics were not associated with either HTN status or ASI user status.

Supplemental Table 2 Potential Prognostic Factors for OS and PFS in Patients With mRCC

	N	OS (mos)			PFS (mos)		
		Median (95% CI)	HR (95% CI)	*P*	Median (95% CI)	HR (95% CI)	*P*
Age, y							
20-59	72	21.3 (12.6-29.9)	1.00		7.2 (5.8-8.6)	1.00	
60-69	115	19.5 (14.0-25.0)	1.06 (0.74-1.51)	.75	7.3 (5.2-9.4)	0.92 (0.67-1.27)	.62
70-92	116	20.9 (16.2-25.6)	1.12 (0.79-1.60)	.52	10.1 (7.1-13.2)	0.83 (0.60-1.14)	.83
Heng criteria							
Favorable	49	42.4 (35.5-49.3)	1.00		24.6 (13.4-35.7)	1.00	
Intermediate	139	22.6 (18.3-26.9)	1.81 (1.19-2.77)	.006	8.5 (6.2-10.9)	2.00 (1.37-2.39)	<.001
Poor	101	8.1 (6.2-10.0)	4.70 (3.02-7.31)	<.001	5.1 (4.1-6.1)	4.08 (2.73-6.12)	<.001
Prior nephrectomy							
No	62	8.2 (6.2-10.0)	1.00		5.3 (3.9-6.7)	1.00	
Yes	241	23.4 (18.2-28.7)	0.36 (0.27-0.50)	<.001	9.4 (6.7-12.1)	0.47 (0.35-0.63)	<.001
No. of metastatic sites							
1	84	29.5 (21.5-37.5)	1.00		13.7 (9.5-17.9)	1.00	
>1	219	15.7 (11.5-20.0)	1.58 (1.16-2.16)	.004	6.7 (5.8-7.6)	1.52 (1.14-2.02)	.004
Histology							
Non—clear-cell	31	13.9 (5.9-21.9)	1.00		5.8 (3.5-8.1)	1.00	
Clear-cell	212	23.1 (17.1-29.1)	0.65 (0.43-1.00)	.05	9.4 (6.5-12.3)	0.61 (0.40-0.91)	.02
HTN at baseline							
No	106	20.1 (15.5-24.7)	1.00		8.2 (5.4-11.0)	1.00	
Yes	197	20.3 (16.4-24.2)	1.09 (0.82-1.45)	.54	8.2 (6.6-9.7)	1.05 (0.81-1.36)	.72
Use of anti-HTN medication at baseline							
No anti-HTN medication	106	20.1 (15.5-24.7)	1.00		8.2 (5.4-11.0)	1.00	
ASI	126	22.3 (18.9-25.7)	1.00 (0.74-1.38)	.96	8.6 (6.3-10.9)	1.00 (0.75-1.32)	.98
Other anti-HTN medication	71	16.5 (10.8-22.2)	1.26 (0.89-1.79)	.20	7.3 (5.0-9.6)	1.15 (0.83-1.59)	.41
Treatment-induced HTN							
No	193	13.9 (10.4-17.4)	1.00		6.4 (5.6-7.3)	1.00	
Yes	110	34.9 (28.2-41.6)	0.41 (0.30-0.55)	<.001	15.6 (11.6-19.7)	0.43 (0.33-0.56)	<.001
ASI use as treatment-related anti-HTN medication							
No	232	16.5 (12.9-20.2)	1.00		6.6 (5.8-7.5)	1.00	
Yes	71	37.7 (26.0-49.5)	0.38 (0.26-0.54)	<.001	16.7 (6.1-27.2)	0.41 (0.30-0.57)	<.001

Abbreviations: ASI = angiotensin system inhibitors; CI = confidence interval; HR = hazard ratio; HTN = hypertension; mRCC = metastatic renal cell carcinoma; OS = overall survival; PFS = progression-free survival.

Supplemental Table 3 Patient Characteristics Among Patients With TKI-induced HTN for ASI Users (n = 91) and ASI Nonusers (n = 19)

	ASI User Status			
	Yes N (%)	No N (%)	*P*	Total N (%)
Total	91	19		110
Gender				
Male	58 (63.7)	9 (47.4)	.20	67 (60.9)
Female	33 (36.3)	10 (52.6)		43 (39.1)
Age, y				
Median	65	66	.56	65
Range	22-89	43-78		22-89
WHO				
0-1	84 (92.3)	18 (94.7)	1.00	102 (92.7)
>1	7 (7.7)	1 (5.3)		8 (7.3)
Prior nephrectomy				
Yes	83 (91.2)	15 (78.9)	.22	98 (89.1)
No	8 (8.8)	4 (21.1)		12 (10.9)
Histology				
Clear-cell	71 (84.5)	13 (86.7)	1.00	84 (84.8)
Non—clear-cell	13 (15.5)	2 (13.3)		15 (15.2)
Missing	7	4		11
No. of metastatic sites				
0-1	30 (33.0)	6 (31.6)	1.00	36 (32.7)
>1	61 (67.0)	13 (68.4)		74 (67.3)
Heng criteria				
Favorable	25 (29.1)	4 (23.5)	.78	29 (28.2)
Intermediate	46 (53.5)	9 (52.9)	1.00	55 (53.4)
Poor	15 (17.4)	4 (23.5)	.51	19 (18.4)
Missing	5	2		7
Treatment				
Sunitinib	73 (86.8)	16 (90.6)	1.00	89 (80.9)
Pazopanib	18 (13.2)	3 (9.4)		21 (19.1)

Abbreviations: ASI = angiotensin system inhibitors; HTN = hypertension; TKI = tyrosine kinase inhibitors; WHO = World Health Organization.