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Angiotensin system inhibitors and outcome of sunitinib treatment in patients with metastatic renal cell carcinoma: A retrospective examination

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ABSTRACT

Background: Sunitinib is a standard treatment for metastatic renal cell carcinoma. Angiotensin system inhibitors, including angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, are widely used in hypertension, kidney disease, and heart failure. Data suggests that they may inhibit tumourigenesis.

Aims: To study the effect of angiotensin system inhibitors on sunitinib treatment outcome in metastatic renal cell carcinoma.

Methods: We performed a retrospective study of an unselected cohort of patients with metastatic renal cell carcinoma who were treated with sunitinib. Patients were divided into angiotensin system inhibitors users (group 1) and non-users (group 2). The effect of angiotensin system inhibitors on objective response, time to disease progression and overall survival, was tested with adjustment for known confounding risk factors through logistic regression model and Cox regression model.

Results: Between 2004 and 2010, 127 patients with metastatic renal cell carcinoma were treated with sunitinib, 44 group 1 and 83 group 2. The groups were balanced regarding known clinicopathologic prognostic factors. Objective response was partial response/stable disease 86% versus 72% and progressive disease 14% versus 28% ($p = 0.07$) in group 1 versus 2, respectively. Median progression free survival was 13 versus 6 months (HR 0.537, $p = 0.0055$), and median overall survival 30 versus 23 months (HR 0.688, $p = 0.21$), in favour of group 1.

Conclusions: Angiotensin system inhibitors may improve the outcome of sunitinib treatment in metastatic renal cell carcinoma. This should be investigated prospectively, and if validated applied in clinical practise and clinical trials.

1. Introduction

Renal cell carcinoma is the most common cancer of the kidney.[1] Thirty percent of patients present with metastatic disease[2,3], and recurrence develops in 40% of patients treated for a localised tumour.[2,4] An understanding of the pathogenesis of renal cell carcinoma at the molecular level, and randomised clinical trials, have established the standard role of the orally administered vascular endothelial growth factor receptor and platelet derived growth factor receptor

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inhibitor sunitinib for the treatment of advanced renal cell carcinoma.[5]

Data suggests that angiotensin II, via activation of the angiotensin II type 1 receptors, stimulates cellular proliferation[6] and migration,[7] and induces angiogenesis by upregulating the vascular endothelial growth factor receptor.[8,9] Therefore, the angiotensin system may be implicated in the tumourigenesis process, and its blockade can represent a novel molecular targeted therapy.[10,11] Angiotensin system inhibitors, including angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, are widely used in the treatment of hypertension, chronic kidney disease, and heart failure. Pre-clinical and clinical studies suggested that blockade of the renin–angiotensin pathway with angiotensin system inhibitors may inhibit tumour growth in several cancer types, including reducing the incidence of advanced adenomatous colon polyps,[12] retarding tumour growth and decreasing the extent of colorectal cancer liver metastases,[13] triggering apoptotic cell death in human pancreatic cancer cells,[14] delaying progression of pancreatic intraepithelial neoplasia and cancer,[15] and increasing survival in patients with advanced non-small cell lung cancer undergoing treatment with platinum based chemotherapy.[16]

In the present study we sought to determine the effect of concomitant angiotensin system inhibitors use on the outcome of patients with metastatic renal cell carcinoma that are treated with sunitinib.

2. Patients and methods

2.1. Study group

Between January 1st 2002 and November 30 2010, 379 patients with histologically confirmed metastatic renal cell carcinoma were registered and seen in the division of medical oncology, Johns Hopkins Kimmel Cancer Center. Of these, 127 patients that were treated with sunitinib, between February 1st 2004 and November 30 2010, comprised the study group. The other 252 patients were treated with therapies other than sunitinib. Data were retrospectively collected from electronic medical records and paper charts, including the following clinicopathologic information: age, gender, tumour histology, the time interval from initial diagnosis to sunitinib treatment initiation, Eastern Cooperative Oncology Group performance status, prior treatments for renal cell carcinoma, sites of metastasis, laboratory findings, pre-treatment and on treatment blood pressure levels, treatment associated side-effects, sunitinib dose reduction and/or interruption, and treatment outcomes including objective response rate, time to disease progression and overall survival. Outcome data was last updated on November 30 2010. Data on the concomitant use of medications, including angiotensin system inhibitors (angiotensin converting enzyme inhibitors and angiotensin II receptor blockers) was gathered from patient's electronic medical records and paper charts documenting baseline patient intake and regular on treatment follow-ups, pharmacy records, and by contacting patients and other treating physicians as needed.

2.2. Sunitinib treatment

All patients had objective disease progression on scans before starting sunitinib treatment. Sunitinib was prescribed as a part of standard treatment or clinical trial. It was administered orally, usually at a starting dose of 50 mg once daily, in 6-week cycles consisting of 4 weeks of treatment followed by 2 weeks without treatment. In patients with significant comorbidities, treatment was initiated at a reduced dose, with subsequent dose escalation if well tolerated. On treatment dose reduction or treatment interruption were done for the management of adverse events, depending on their type and severity, according to standard guidelines. Treatment was continued until evidence of disease progression on scans, unacceptable adverse events, or death. Patient follow-up generally consisted of regular physical examinations and laboratory assessments (haematologic and serum chemical measurements), every 4–6 weeks, and imaging studies performed every 12–18 weeks.

2.3. Treatment outcomes

Follow-up time was defined as the time from sunitinib treatment initiation to November 30 2010. For the evaluation of response, the Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 was applied.[17] The response was assessed by independent radiologists and treating physicians, and personally reviewed by the investigator D.K. Progression free survival was determined by the investigator D.K., and defined as the time from the initiation of sunitinib treatment until evidence of disease progression on scans or death of any cause. Overall survival was defined as the time from the initiation of sunitinib treatment to death of any cause. Treatment associated toxicity was evaluated according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 3.0.

2.4. Statistical analysis

The group of angiotensin system inhibitor users included patients that started angiotensin system inhibitors before or within 1 month after beginning sunitinib treatment. To better elucidate the effect of angiotensin system inhibitors use, baseline clinical characteristics and known prognostic factors were compared between angiotensin system inhibitors users versus non-users to identify any potential confounding covariates. Chi-square test was used to compare categorical end-points, and two-sample *t*-test was used to compare continuous end-points after necessary data transformation. Known prognostic factors in metastatic renal cell carcinoma treated with sunitinib[18–21] were included as confounding covariates in the analysis, including past nephrectomy, clear cell versus non-clear cell kidney cancer histology type, time from initial kidney cancer diagnosis to sunitinib treatment initiation, the presence of more than two metastatic sites, lung/liver/bone metastasis, Eastern Cooperative Oncology Group performance status, the presence of anaemia and corrected (for albumin) serum calcium level above 10 mg/dL, platelet count, sunitinib induced hypertension, past cytokines

and/or targeted treatments, percentage of patients that had dose reduction and/or treatment interruption, and mean dose/cycle. Patients who did not progress or die by November 30 2010 were censored in progression free survival analysis and overall survival analysis, respectively. Toxicities were estimated by proportions. Logistic regression was used to compare binary indicator of objective response and Cox regression was used to compare time to progression and time to death. Regression tree and graphical exploratory techniques were used to select most influential covariates to be included in the model fitting. Since a common approach in metastatic renal cell carcinoma is to use one prognostic model, the analysis was further stratified by the Heng prognostic model.[22] Finally, a multivariate analysis of the above mentioned prognostic factors was done for the entire patient cohort, to determine if the use of angiotensin system inhibitors is independently associated with progression free survival. Data were analysed using S-Plus 8.0 for Windows Enterprise Developer.

2.5. *Regulatory considerations*

The research was carried out in accordance with the approval by the IRB committee of our institution.

3. Results

3.1. *Patient characteristics*

One hundred and twenty-seven patients (age 60.7 ± 11.4 years, mean ± SD; male 71%, $n = 90$) with metastatic renal cell carcinoma that were treated with sunitinib between February 1st 2004 and November 30 2010. 82% of the patients ($n = 104$) were treated and followed with sunitinib at Johns Hopkins Kimmel Cancer Center. 18% of the patients ($n = 23$) were treated with sunitinib at other institutions, and came to Johns Hopkins Kimmel Cancer Center for recommendations and further treatments after progression on sunitinib. Their data from medical records, scans, and pharmacy records were personally reviewed by the investigator D.K. that also interviewed the patients and contacted their treating physicians as needed. 44 patients were angiotensin system inhibitors users (group 1, 29 angiotensin converting enzyme inhibitors users and 15 angiotensin II receptor blockers users) and 83 non-users (group 2). With regard to sunitinib treatment initiation time, 42 users started angiotensin system inhibitors before sunitinib, and 2 users within 1 month of sunitinib. All 44 users were on angiotensin system inhibitors during the whole sunitinib treatment period. Amongst the 83 non-users, only one patient started an angiotensin system inhibitor after 4 months on sunitinib. The distribution of clinicopathologic factors is shown in Table 1. The groups were balanced regarding the presence of the following known clinicopathologic prognostic factors[18–21]: past nephrectomy, clear cell versus non-clear cell kidney cancer histology type, time from initial kidney cancer diagnosis to sunitinib treatment initiation, the presence of more than two metastatic sites, presence of lung/liver/bone metastasis, Eastern Cooperative Oncology Group performance status, the presence of anaemia and corrected (for albumin) serum calcium level above 10 mg/dL, platelets count, and sunitinib induced hypertension. The distribution of subgroups according to the Heng prognostic model[22] was similar ($p = 0.98$) between angiotensin system inhibitors users versus non-users, and shown in Table 1. LDH values were available in only 30% of the patients ($n = 43$), 12 users of angiotensin system inhibitors and 31 non-users). In this subgroup of patients with available LDH values, a high serum LDH (>1.5 times upper limit of normal) was noted in 25% ($n = 3/12$) and 9% ($n = 3/31$) of angiotensin system inhibitors users and non-users, respectively ($p = 0.54$). Finally, the groups were also balanced regarding past cytokines and/or targeted treatments, percentage of patients that had sunitinib dose reduction and/or treatment interruption, and mean sunitinib dose/cycle. Nine patients had CNS metastases, 3 were angiotensin system inhibitors users and 6 non-users. Amongst these, 8 patients got sunitinib as their first line of systemic therapy, and one patient (an angiotensin system inhibitors user) got sunitinib as a third line systemic therapy (after first line interferon and second line bevacizumab). The starting dose of sunitinib was usually 50 mg once daily, in 6-week cycles consisting of 4 weeks of treatment followed by 2 weeks without treatment. All patients received treatment in the 4/6 week schedule. In 4 patients, all users of angiotensin system inhibitors, the starting dose was lower due to comorbidities, including AIDS (one patient, starting dose 25 mg) and chronic renal failure (3 patients, starting dose 37.5 mg).

3.2. *Sunitinib treatment outcomes*

Due to the small number of 15 angiotensin II receptor blockers recipients, all analyses were performed only for the combined group of angiotensin system inhibitors (angiotensin converting enzyme inhibitors users and angiotensin II receptor blockers users). Objective response in angiotensin system inhibitors users versus non-users was partial response/stable disease 86% versus 72%, and progressive disease at first imaging evaluation within the first 3 months 14% versus 28% ($p = 0.07$). Recipients of angiotensin system inhibitors had a doubling of median progression free survival versus non-recipients (13 versus 6 months, HR 0.537, $p = 0.0055$, Fig. 1). Median overall survival was 30 versus 23 months (HR = 0.688, $p = 0.21$, Fig. 2) in angiotensin system inhibitors users versus non-users, respectively. Subgroups analysis according to the Heng prognostic model[22], and of patients with mRCC of the clear cell variety that were naïve to systemic targeted treatment ($n = 87$, 32 angiotensin system inhibitors users and 55 non-users that were balanced regarding the above mentioned clinicopathologic prognostic factors) in terms of response rate, progression free survival, and overall survival, is shown in Table 2. Zoledronic acid was utilised in 12 patients (9%), 5 were users of angiotensin system inhibitors (median progression free survival 3 months), and 7 non-users (median progression free survival 2 months). Finally, in a multivariate analysis of the above mentioned prognostic factors amongst the entire patient cohort, 4 Clinicopathologic factors that were found to be independently associated with progression free survival are the use of angiotensin system inhibitors (HR = 0.54, $p = 0.02$), past nephrectomy (HR = 0.35, $p < 0.001$), clear cell histology (HR = 0.31, $p = 0.03$), and sunitinib induced hypertension (HR = 0.59, $p = 0.03$). Clinicopathologic factors that were not independently associated

Table 1 – Distribution of clinicopathologic prognostic factors.

Characteristics	ASIs users ($n = 44$)	ASIs non-users ($n = 83$)	P
Age (years): mean ± SD (range; median)	64.4 ± 8 (47–79; 66)	58.7 ± 12.4 (24–85; 60)	0.004
Tumour histology			
Clear cell	84% ($n = 37$)	77% ($n = 64$)	0.49
Non-clear cell	16% ($n = 7$)	23% ($n = 19$)	
ECOG PS: 0–1	91% ($n = 40$)	89% ($n = 74$)	0.85
>1	9% ($n = 4$)	11% ($n = 9$)	
Past nephrectomy	86% ($n = 38$)	84% ($n = 70$)	0.96
Time (months) from dx to sunitinib treatment: mean ± SD (range; median)	32.1 ± 39.8 (1–168; 13)	30.5 ± 43.5 (1–180; 11)	0.84
Prior systemic treatment	32% ($n = 14$)	30% ($n = 25$)	0.98
Prior targeted treatments			
None	84% ($n = 37$)	84% ($n = 70$)	0.93
One	16% ($n = 7$)	15% ($n = 12$)	
Two	0%	1% ($n = 1$)	
Lung metastasis	68% ($n = 30$)	69% ($n = 57$)	0.89
Liver metastatis	30% ($n = 13$)	24% ($n = 20$)	0.65
Bone metastasis	34% ($n = 14$)	36% ($n = 30$)	0.97
$\geqslant$2 metastatic sites	84% ($n = 37$)	77% ($n = 64$)	0.49
Anaemia	55% ($n = 24$)	52% ($n = 43$)	0.9
Platelets count: mean ± SD (range; median)	264 ± 108 (122–538; 247)	291 ± 122 (114–934; 273)	0.23
Corrected calcium > 10 mg/dL	18% ($n = 8$)	17% ($n = 14$)	0.96
Sunitinib induced HTN	57% ($n = 25$)	53% ($n = 44$)	0.82
Sunitinib dose reduction/treatment interruption	55% ($n = 24$)	46% ($n = 38$)	0.45
Mean sunitinib dose (mg)/treatment cycle: mean ± SD (range; median)	41.8 ± 9.3 (17–50; 42)	44.1 ± 8.9 (12–50; 50)	0.18

Abbreviations: SIs = angiotensin system inhibitors; Dx = diagnosis; ECOG PS = Eastern Cooperative Oncology Group performance status; HTN = hypertension.

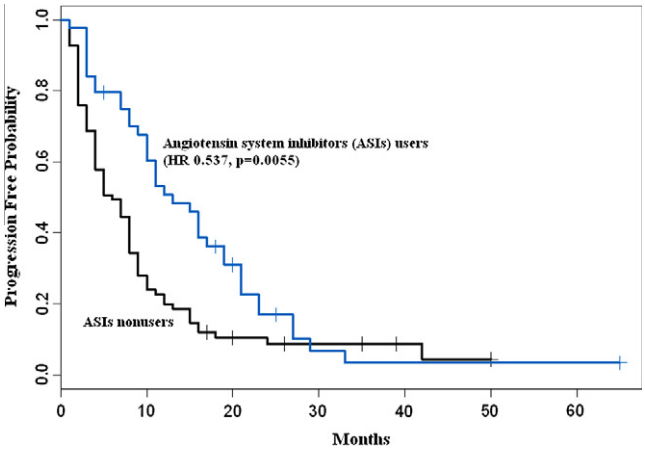

Fig. 1 – Kaplan–Meier curves showing progression-free survival, stratified by the use of angiotensin system inhibitors.

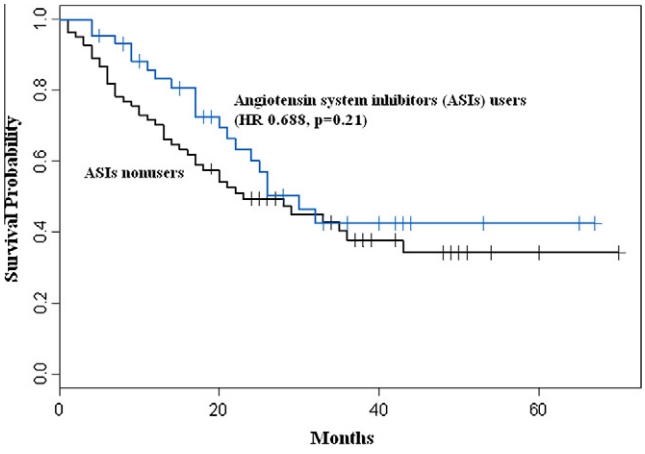

Fig. 2 – Kaplan–Meier curves showing overall survival, stratified by the use of angiotensin system inhibitors.

with progression free survival are the Heng risk stratification, time from initial kidney cancer diagnosis to sunitinib treatment initiation, the presence of more than two metastatic sites, lung/liver/bone metastasis, Eastern Cooperative Oncology Group performance status, the presence of anaemia and corrected (for albumin) serum calcium level above 10 mg/dL, platelet count, past cytokines and/or targeted treatments, percentage of patients that had dose reduction and/or treatment interruption, and mean dose/cycle.

3.3. *Treatment associated toxicity*

The distribution and grading of adverse events is shown in Table 3. The most common adverse events were fatigue (58%, $n = 74$), neutropenia (43%, $n = 55$), diarrhoea (43%, $n = 54$), thrombocytopenia (41%, $n = 53$), mucositis (38%, $n = 48$), nausea and vomiting (33%, $n = 42$), and hand-foot syndrome (29%, $n = 37$). Grade 3/4 toxicity events occurred in 25% ($n = 11$) of angiotensin system inhibitors users versus 27% ($n = 22$) of non-users. A total of 55% ($n = 24$) of patients using

Table 2 – Sunitinib treatment outcomes.

Characteristic/group (number of patients)	ASIs* users	ASIs non-users	HR, *p*
Whole patient group			
	n = 44	*n* = 83	
Objective response% (*n*)			
Partial response/stable disease	86% (*n* = 38)	72% (*n* = 60)	*p* = 0.07
Progressive disease**	14% (*n* = 6)	28% (*n* = 23)	
Median progression free survival (months)	13	6	HR 0.537, *p* = 0.0055
Median overall survival (months)	30	23	HR 0.688, *p* = 0.21
Heng favourable risk			
	n = 12	*n* = 21	
Objective response% (n)			
Partial response/stable disease	100% (*n* = 12)	81% (*n* = 17)	*p* = 0.29
Progressive disease	0% (*n* = 0)	19% (*n* = 4)	
Median progression free survival (months)	12	6.5	HR 0.6, *p* = 0.25
Median overall survival (months)	20.5	17	HR 0.52, *p* = 0.26
Heng intermediate risk			
	n = 24	*n* = 47	
Objective response% (*n*)			
Partial response/stable disease	87% (*n* = 21)	68% (*n* = 32)	*p* = 0.14
Progressive disease	13% (*n* = 3)	32% (*n* = 15)	
Median progression free survival (months)	12	5	HR 0.52, *p* = 0.014
Median overall survival (months)	21	17	HR 1.1, *p* = 0.97
Heng poor risk			
	n = 8	*n* = 15	
Objective response% (*n*)			
Partial response/stable disease	62% (*n* = 5)	73% (*n* = 11)	*p* = 0.95
Progressive disease	38% (*n* = 3)	27% (*n* = 4)	
Median progression free survival (months)	12.5	7	HR 0.38, *p* = 0.06
Median overall survival (months)	23	15	HR = 0.14, *p* = 0.18
Patients of the clear cell variety that were naïve to systemic targeted treatment			
	n = 32	*n* = 55	
Objective response% (*n*)			
Partial response/stable disease	91% (*n* = 29)	85% (*n* = 47)	*p* = 0.7
Progressive disease	9% (*n* = 3)	15% (*n* = 8)	
Median progression free survival (months)	12	6	HR = 0.65, *p* = 0.07
Median overall survival (months)	21	17	HR = 0.9, *p* = 0.78

* ASIs = angiotensin system inhibitors.

** At first imaging evaluation within the first 3 months.

angiotensin system inhibitors and 46% (*n* = 38) of the non-users (*p* = 0.45, Table 1) had a dose reduction and/or treatment interruption because of adverse events. 20% (*n* = 9) versus 7% (*n* = 6) of the patients in each group had to stop sunitinib treatment due to dose limiting toxicity.

3.4. *Impact of other medications and pre-existing hypertension*

There was no significant progression free survival and overall survival benefit for patients receiving beta blockers, calcium channels blockers, or amongst patients with pre-existing hypertension, in the whole patient group as well as in subgroup analysis of angiotensin system inhibitors users and non-users.

4. Discussion

The present study suggests that concomitant use of angiotensin system inhibitors may improve the outcome of sunitinib treatment in metastatic renal cell carcinoma. In this retrospective study, patients receiving angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, before or within one month of sunitinib treatment, had a a significant (HR 0.537, *p* = 0.0055) 7 months increase of the progression free survival, after adjustment for other known risk factors for poorer outcome. At present, progression free survival is considered to be a valid measure of clinical benefit in patients with metastatic renal cell carcinoma treated with targeted compounds.[23,24] Patients using angiotensin system inhibitors also had an increase in response rate (47% versus 37%), a decrease of primary treatment refractoriness (progressive disease at first imaging evaluation within the first 3 months, 14% versus 28%), and better overall survival (HR 0.688), although these were not statistically significant at 0.05 significance level (might have been in a larger patient cohort). Furthermore, subgroups analysis of patients according to the Heng prognostic model[22] and those with clear cell variety that were naïve to systemic targeted treatment, revealed a better progression free survival and hazard ratio of patients

Table 3 – Sunitinib treatment associated adverse events.

Adverse event	ASIs* users ($n = 44$)		ASIs non-users ($n = 83$)	
	All grades	Grades 3/4	All grades	Grades 3/4
Abdominal discomfort	9% ($n = 4$)	0%	18% ($n = 15$)	0%
Anaemia	23% ($n = 10$)	2% ($n = 1$)	48% ($n = 40$)	6% ($n = 5$)
Bleeding (epistaxis, gastrointestinal, haematuria)	14% ($n = 6$)	5% ($n = 2$)	12% ($n = 10$)	0%
Change of taste	20% ($n = 9$)	0%	12% ($n = 10$)	0%
Decrease of appetite	11% ($n = 5$)	0%	8% ($n = 7$)	0%
Constipation	5% ($n = 2$)	0%	1% ($n = 1$)	0%
Cough	5% ($n = 2$)	0%	1% ($n = 1$)	0%
Diarrhoea	55% ($n = 24$)	7% ($n = 3$)	36% ($n = 30$)	6% ($n = 5$)
Oedema	5% ($n = 2$)	0%	5% ($n = 4$)	0%
Fatigue	57% ($n = 25$)	5% ($n = 2$)	59% ($n = 49$)	7% ($n = 6$)
Hand-foot syndrome	36% ($n = 16$)	2% ($n = 1$)	25% ($n = 21$)	4% ($n = 3$)
Increased bilirubin	9% ($n = 4$)	0%	8% ($n = 7$)	0%
Increased creatinine	14% ($n = 6$)	5% ($n = 2$)	8% ($n = 7$)	0%
Mucositis	43% ($n = 19$)	7% ($n = 3$)	35% ($n = 29$)	7% ($n = 6$)
Nausea/vomiting	32% ($n = 14$)	2% ($n = 1$)	34% ($n = 28$)	4% ($n = 3$)
Neutropenia	45% ($n = 20$)	11% ($n = 5$)	42% ($n = 35$)	8% ($n = 7$)
Skin toxicity	18% ($n = 8$)	0%	30% ($n = 25$)	1% ($n = 1$)
Thrombocytopenia	41% ($n = 18$)	5% ($n = 2$)	42% ($n = 35$)	4% ($n = 3$)
Venous thromboembolism	2% ($n = 1$)	2% ($n = 1$)	0%	0%

* ASIs = angiotensin system inhibitors.

using angiotensin system inhibitors, although this was not statistically significant at 0.05 significance level in some of the subgroups representing a relatively small cohort. Finally, in a multivariate analysis for the entire group, which included the clinicopathologic prognostic factors mentioned before, the use of angiotensin system inhibitors was independently associated with progression free survival (HR = 0.54, $p = 0.02$).

The present study observation is supported by existing preclinical and clinical data suggesting that blockade of the renin–angiotensin pathway with angiotensin system inhibitors may inhibit tumour growth in several cancer types, by inhibiting the activation of angiotensin II type 1 receptors, and therefore tumour cell proliferation, migration, and angiogenesis. Some of these effects may be mediated by mechanisms that are independent of sunitinib action as decreasing the level of the vascular endothelial growth factor, modulating matrix metalloproteinases activity, reducing the activation of the epidermal growth-factor receptor, and inhibiting the mitogen-activated protein kinase/signal transducers and activators of transcription (MAPK/STAT) pathway.[6–16] Therefore angiotensin system inhibitors may be additive or synergistic with VEGF inhibition therapy, and not be specific to sunitinib treatment.

Our study has some limitations. This is a retrospective study that represents a heterogeneous group of patients, including all histological variants of renal cell carcinoma, and patients who were treatment naïve and those with a history of prior therapy. This is because the study was designed to generate an initial hypothesis, and to evaluate a potential signal of antitumour activity and benefit of angiotensin inhibitors in patient's metastatic renal cell carcinoma that are treated with sunitinib. Therefore we included an unselected cohort of all patients that were treated with sunitinib. Furthermore, previous data suggests that progression-free survival is not necessarily affected by targeted therapy administered as first- or second-line[22], and although sunitinib has been less extensively studied in patients with non-clear cell carcinoma, data suggests that it may be active in patients with non-clear cell histology.[20,25] The median progression free survival in the group not receiving angiotensin system inhibitors is shorter than expected.[5] We are unable to exclude the possibility that unequal distribution of unidentified clinicopathologic parameters in our patient cohort may have biased the observed results. In addition, the total number of 44 patients treated with angiotensin system inhibitors is relatively small. Other clinicopathologic factors that were not found to be significantly associated with disease progression in the present study might have been important in a larger patient cohort, as the Heng risk stratification, time from initial kidney cancer diagnosis to sunitinib treatment initiation, the presence of more than two metastatic sites, and the presence of anaemia and corrected (for albumin) serum calcium level above 10 mg/dL. Finally, all users in the present study started angiotensin system inhibitors before (95%, $n = 42/44$) or shortly after (within a month, 5%, $n = 2/44$) initiation of sunitinib treatment. Therefore, the benefit of adding angiotensin system inhibitors after this period of time remains an open question.

Despite these limitations, our clinical observation that angiotensin system inhibitors seem to improve the outcome of sunitinib treatment in metastatic renal cell carcinoma might contribute to treatment decisions, patient selection, and clinical trials design. There were no inadvertent interactions observed in patients receiving angiotensin system inhibitors concurrently with sunitinib. Because of little side-effects and relatively low costs, further studies may be warranted, to test and confirm our hypothesis generating observation in larger patient cohorts, to elucidate the underlying molecular mechanisms, and to define which subgroup of patients (e.g. according to risk by prognostic models, clear cell versus non-clear cell histology, and first line versus advanced line treatment) will benefit. These may include retrospective

subgroup analysis of previously completed large randomised trials of sunitinib or other VEGF inhibitors therapy in metastatic renal cell carcinoma, as well as prospective studies with addition of angiotensin system inhibitors to standard antineoplastic targeted therapies.

Conflict of interest statement

None declared.

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