

Hypertension and angiotensin system inhibitors in patients with metastatic renal cell carcinoma

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Abstract

Arterial hypertension (HTN) is a class effect of anti-vascular endothelial growth factor (VEGF) therapies, including the monoclonal antibody bevacizumab. Data are conflicting regarding the role of the renin-angiotensin system on angiogenesis and recent data suggest that the use of angiotensin system inhibitors (ASIs; angiotensin receptor blockers or angiotensin-converting enzyme inhibitors) is associated with improved survival in metastatic renal cell carcinoma (mRCC), particularly when used with VEGF targeted therapies. The aim of this review is to discuss the available treatment options for mRCC and associated incidence of hypertension as well as summarize the known data about ASIs use and mRCC. Additionally, given that the optimal management of HTN remains unclear, we will focus on prevention strategies and propose potential therapeutic approaches.

Introduction

Hypertension (HTN) is one of the most commonly found comorbidity in cancer patients and at the same time being known as an established risk factor for renal disease and renal cell carcinoma (RCC).^{1,2} Patients with metastatic RCC (mRCC), compared with those with non-

RCC malignancies, have a significantly higher incidence of HTN.^{3,4} In fact, HTN can be regarded as one of the most frequently observed class-, as well as dose-dependent adverse events of vascular endothelial growth factor/receptor (VEGF/VEGFR) inhibitors, also representing the best-documented one.⁵ The risk and the severity of HTN related to VEGF inhibitors (VEGFi) depend on the type of drug, dose and schedule used, age of patients and the presence of cardiac disease. Considering the same drug, it is also higher in patients with mRCC compared with other cancers as reported with sorafenib,⁶ sunitinib⁷ and axitinib⁸ phase III trials but surprisingly not in those with pazopanib.⁹ As a known class-specific side effect for anti-VEGF agents, HTN has been reported as predictive of better outcome and as a potential biomarker, especially with axitinib, to guide dose adjustments for individual patients.¹⁰ Even though pre-existing HTN has been reported as a prognostic factor in mRCC treated with VEGFi,^{11,12} its recognition is an important issue because poorly controlled HTN could lead to serious vascular events. For example, a higher incidence of intracerebral hemorrhage has been reported in patients with mRCC treated with tyrosine kinase inhibitors (TKI), probably related to uncontrolled HTN at diagnosis.¹³ Optimal anti-hypertension medication has not yet been defined. This paper will discuss HTN and its management strategies, as reported in pivotal studies, and in the literature, with a focus on angiotensin system inhibitors (ASI).

Prevalence of hypertension caused by angiogenic inhibitor agents in renal cell carcinoma trials

Although HTN is a very frequent adverse effect among cancer patients treated with VEGFi, the exact prevalence and the risk of HTN in RCC patients who receive these drugs have not yet been specified. The reported incidence of all-grade HTN ranges from 25% with sorafenib and sunitinib to 42% with pazopanib and axitinib.^{6-8,14} Table 1^{6-8,14-20} summarizes the findings of available options in phase III studies in RCC concerning HTN. Bevacizumab represents a monoclonal antibody targeting the VEGF pathway.²¹ The approval of bevacizumab in RCC patients was based on the results from the AVOREN trial¹⁷ and the CALGB 90206 trial.¹⁸ The toxicities of anti-VEGF therapy observed in these studies included proteinuria, bleeding and HTN, as previously observed in other malignancies. Specifically, in the AVOREN and in the CALGB 90206 trials the incidence of HTN was 26% and 28% in the bevacizumab plus interferon arm, whereas the grade 3 or 4 incidence of HTN was noted as 6% and 11%, respectively.¹⁹ In a meta-analysis, referring to over 12,000 patients treated for different solid tumors in phase II or III clinical trials,²² the overall incidence of all blood pressure (BP) elevation events was 24% [95% confidence interval (CI), 20-

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29%] among patients receiving bevacizumab and the incidence of grade 3 or 4 HTN was found in 8% of patients (95% CI, 6-10%).²² Moreover, a previously published meta-analysis of over 1800 patients, reported bevacizumab administration being correlated with a significant dose-dependent increase in the risk of HTN.²³ Interestingly, in this study two groups of patients (with RCC and breast cancer), showed the highest relative risk of HTN development; it may indicate that HTN incidence may be associated with cancer type. Sorafenib is a multi-targeted TKI, which affects Raf-kinase, VEGFR-1, -2 and -3, platelet-derived growth factor receptor (PDGFR)- β , FMS like tyrosine kinase 3 (FLT-3), c-KIT and RET receptor tyrosine kinase.²⁴ In RCC patients previously treated with cytokines, sorafenib was compared with placebo in the TARGET trial. In this case, sorafenib exhibited a higher incidence of all grade HTN (17%), but only 4% of grade 3 or 4 HTN.⁶ Furthermore, in a meta-analysis of over 4500 patients (with different cancers) participating in clinical trials of sorafenib, an overall incidence of HTN (all grades) of 23.4% (95% CI, 16.0-32.9%) was shown while the incidence of grade 3 or 4 HTN was 5.7% (95% CI, 2.5-12.6%). Sorafenib was positively correlated with the increased risk of HTN (all grades) manifestation [relative risk (RR)=6.11, 95% CI, 2.44-15.32; P<0.001].²⁵ Indeed, the largest meta-analysis in several solid cancer patients treated with sorafenib, involved 13,555 patients treated in a total of 14 randomized controlled trials and 39 prospective single-arm trials and it showed that the relative risk of all-grade and high-grade HTN associated with sorafenib was 3.07 (95% CI, 2.05-4.60; P<0.01) and 3.31 (95% CI, 2.21-4.95; P<0.01), respectively. The overall incidence of sorafenib-induced all-grade and high-grade HTN was 19.1% (95% CI, 15.8-22.4%) and 4.3% (95% CI, 3.0-5.5%), respectively. Finally, a significantly higher incidence of HTN was also noted in patients with RCC compared with those with non-RCC malignancies (all-grade: 24.9% (95% CI, 19.7-30.1%) vs 15.7% (95% CI, 12.1-19.3%); P<0.05; high-grade: 8.6% (95% CI, 6.0-11.2%) vs 1.8% (95% CI, 0.9-2.6%); P<0.05).³

Sunitinib is a multi-target TKI with inhibitory effects on multiple tyrosine kinase receptors, including VEGFR-1, -2 and -3, PDGFR- α and - β , FLT-3, c-KIT, and RET receptor tyrosine kinase.²⁶ In RCC patients, sunitinib compared to Interferon, provided a significant improvement in progression-free survival (PFS) (11 vs 5 months) in treatment naïve patients at the expense of 24% of all grade HTN and 8% of high grade

HTN.⁷ A meta-analysis by Zhu *et al.* of nearly 5000 patients on sunitinib for the treatment of RCC and gastrointestinal stromal tumors, showed that all grade incidence of HTN was 21.6% (95% CI=18.7-24.8%) while the incidence of grade 3 or 4 HTN was 6.8% (95% CI=5.3-8.8%).²⁷ Sunitinib was also correlated with a significant increase in the relative risk of grade 3 or 4 HTN (RR=22.72, 95% CI=4.48-115.29; P<0.001) and similarly with the above studies for bevacizumab, there was a statistically significant difference between the incidence of all-grade and high-grade HTN in RCC patients and non-RCC patients (RR 1.32, 95% CI, 1.18-1.48%; P<0.001 and RR 1.57, 95% CI, 1.22-2.02%; P=0.001, respectively).

Similarly, Pazopanib is a multi-target TKI, targeting VEGFR-1, -2 and -3, PDGFR- α and - β , and c-KIT.^{28,29} The therapeutic efficacy of pazopanib in patients with mRCC has been demonstrated in three phase III randomized controlled trials: the VEG105192¹⁴ and COMPARZ trials,¹⁵ and a crossover trial (PISCES)¹⁶ investigating patient preference. In the VEG105192 double-blind efficacy trial, treatment-naïve or cytokine-pretreated patients received either pazopanib 800 mg once daily or placebo. The study reported a 40% of incidence in all grade HTN and 13% of incidence in high-grade HTN with pazopanib. The open-label, non-inferiority COMPARZ trial compared the efficacy and safety of pazopanib and sunitinib as first-line therapy in 1110 patients with clear-cell mRCC. The phase IIIb PISCES trial was a double blind, crossover study evaluating patient preference for sunitinib or pazopanib. Patients with mRCC were randomly assigned to pazopanib 800 mg/day for 10 weeks, then a 2-week washout followed by sunitinib 50 mg/day for 10 weeks (4 weeks on, 2 weeks off, 4 weeks on), or the reverse sequence. In both studies, regarding the two groups of patients, no statistically significant differences in grade 3 and 4 HTN or in the overall grade HTN was observed (Table 1).^{6-8,14-20} Indeed, a meta-analysis of over 1600 patients showed that the risk of HTN (all grades) in patients who follow pazopanib therapy (RR=4.97, 95% CI, 3.38-7.30; P<0.001) was even higher than in patients treated with sunitinib (RR=2.20, 95% CI, 1.92-2.52; P<0.001) or sorafenib (RR=1.99, 95% CI, 0.96-1.53; P<0.001). In addition, the overall incidence of pazopanib-associated HTN (all grades) was 35.9% (95% CI, 31.5-40.6%) and HTN (grade 3 or 4) was 6.5% (95% CI, 5.2-8.0%). In contrast with a similar observation of sunitinib therapy, a statistically significant difference

Table 1. Hypertension related to available options in phase III studies in renal cell carcinoma.

Agent	Reference	Regimen	Patient, n	Hypertension (%)	
				All grade	Grade 3/4
Sorafenib	Escudier <i>et al.</i> ⁶	Placebo	452	2	<1
		Sorafenib, 400 mg twice day	451	17	4
Sunitinib	Motzer <i>et al.</i> ⁷	IFN	360	1	1
		Sunitinib, 50 mg/day	375	24	8
Pazopanib	Sternberg <i>et al.</i> ¹⁴	Placebo	145	10	<1
		Pazopanib	290	40	13
Pazopanib	Motzer <i>et al.</i> ¹⁵	Sunitinib	553	41	15/<1
		Pazopanib	557	46	15/<1
Pazopanib	Escudier <i>et al.</i> ¹⁶	Sunitinib	148	26	9/0
		Pazopanib	153	23	8/0
Bevacizumab	Escudier <i>et al.</i> ¹⁷	Placebo + IFN	322	9	<1
		IFN + bevacizumab 10 mg/kg	327	26	3
Bevacizumab	Rini <i>et al.</i> ^{18,19}	Placebo + IFN	349	28	0
		IFN + bevacizumab 10 mg/kg	366	4	11
Axitinib	Rini <i>et al.</i> ⁸	Sorafenib	355	29	10.7/<1
		Axitinib	359	40.4	15.3/<1
Cabozantinib	Motzer <i>et al.</i> ²⁰	Everolimus	332	7	3
		Cabozantinib	331	37	1

IFN, interferon.

between the incidence of pazopanib-induced HTN in RCC and non-RCC patients could not be demonstrated. Axitinib is a selective TKI inhibitor of VEGFR-1, -2 and -3.³⁰ In patients with mRCC on axitinib, HTN had an incidence of 42% (17% had a grade 3) in the phase III AXIS trial.³¹ In a meta-analysis including 10 clinical trials, HTN rate in 1908 axitinib-treated patients, was 40.1% (95% CI, 30.9, 50.2%) and 13.1% (95% CI, 6.7, 24.0%) for all grade and grade 3 or 4, respectively. Considering only the RCC patients, the use of axitinib was associated with an increased risk of developing all grade and high grade hypertension compared to non-RCC patients and the overall incidence of high grade HTN with axitinib was higher than with the other VEGFR-TKI.⁴ The incidence rate of treatment-induced HTN associated with axitinib seems to be higher than those described for all multi-targeted inhibitor. Finally, cabozantinib, a targeted agent against MET and VEGFR-2, has shown promising results and could become another second line option for patients with RCC. Also for cabozantinib in patient with RCC, the most common grade 3 or 4 adverse event was HTN (15%) in the pivotal trial METEOR, while the overall incidence of HTN (all grade) was 37%.²⁰ In patient with metastatic thyroid cancer, treated with cabozantinib in the phase III trial, the overall incidence of HTN and grade 3-4 of HTN were lower than those observed for RCC (32.7 % and 8.4%, respectively).³²

Pathogenesis of hypertension

Although the exact mechanism by which VEGF pathway inhibitors lead to a rise in BP is not fully understood, key hypotheses have been generated. Inhibition of endothelial nitric oxide (NO) synthase, increased vascular stiffness, activation of the endothelin-1 system and inhibition of the renin-angiotensin system have been implicated.^{11,33} The HTN induced by antiangiogenic drugs is probably related to an increase in systemic vascular resistance (SVR). Mechanisms inducing high SVR include neurohormonal factors (such as renin, and aldosterone, catecholamines, epinephrine, norepinephrine, endothelin I), vascular rarefaction (decrease in the density of microvessels), and endothelial dysfunction associated with a decrease in NO production and an increase in oxidative stress. An important part of the mechanism of HTN associated with VEGF inhibition is thought to involve decreased production of NO in the wall of arterioles and other resistance vessels. VEGF increases NO synthesis through upregulation of endothelial NO synthase, and VEGF inhibition diminishes NO synthesis.^{34,35} Indeed, the inhibition of VEGF may cause increased SVR^{36,37} and vascular rarefaction³⁸ leading to HTN. Furthermore, VEGF inhibition may induce renal thrombotic microangiopathy leading to HTN.³⁹

Angiotensin system inhibitors in renal cell carcinoma

There has been experimental evidence that angiotensin II is involved in promoting cancer development. Angiotensin II is a powerful mitogen and facilitates cellular growth and proliferation through transforming growth factor- β ⁴⁰ epidermal growth factor and tyrosine kinase. Angiotensin II also regulates apoptotic mechanisms and angiogenesis by up-regulating VEGF expression⁴¹ stimulating neovascularization⁴² and DNA synthesis⁴³ which is a requirement for tumor growth.⁴⁴ ASI including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), are commonly used as anti-hypertensive and anti-proteinuric agents. There is significant evidence that ASI may have induced cytostatic effects on the cultures of several lines of neoplastic cells and also delayed the growth of differ-

ent types of tumors in a variety of experimental animals.⁴⁵⁻⁴⁸ These drugs were found to suppress the signal transduction mediated by growth factors through AT1R antagonism⁴⁹ and to inhibit the proliferation of cancer cells through activation of the peroxisome proliferator-activated receptor- γ .⁵⁰ Additionally, studies of human clear-cell RCC have demonstrated that angiotensin II receptor expression strongly correlates with tumor aggressiveness and decreased survival.⁵¹ Since that time, several retrospective studies have investigated the association between ASIs and cancer progression and survival. A meta-analysis comparing the use and nonuse of ACEIs or ARBs in several cancer patients (4964 patients treated in a total of 11 trials) showed that the use of ACEIs or ARBs resulted in a significant improvement in disease free survival [hazard ratio (HR) 0.60; 95% CI, 0.41-0.87; P=0.007] and overall survival (OS) (HR 0.75; 95% CI 0.57-0.99; P=0.04). Analysis according to cancer type showed benefits in urinary tract cancer (HR 0.22), colorectal cancer (HR 0.22), pancreatic cancer (HR 0.58), and prostate cancer (HR 0.14), but not in breast cancer and hepatocellular cancer. This meta-analysis provides evidence that the use of ACEIs or ARBs in cancer patients can lead to a 40 and 25% reduction in the risk of cancer recurrence and mortality.⁵² Furthermore, there seems to be a synergistic interaction between ASIs and VEGF-targeted therapy given that these agents are thought, at least in part, to augment a similar pathway. In a murine xenograft model of RCC, the combination of sunitinib and telmisartan, compared to sunitinib alone, revealed an enhancement of the blockage of the VEGF pathway on renal tumor resulting in a decrease in neoangiogenesis and an increase in necrosis.⁵³ Recent clinical evidences suggest that use of ASI and ARB may be associated with improved outcomes in kidney cancer patients particularly when they are used with VEGF therapies. Three prior studies have reported on a significant association of ASI use (at baseline or within first 30 days of VEGF-targeted therapy) and survival for patients with mRCC using a VEGF-targeted therapy. The first compared ASI users *vs* non-users in a cohort of 127 patients with mRCC treated with sunitinib and found a significant association with PFS (HR 0.54, P=0.0055, medians of 13 *versus* 6 months) and a non-statistically significant improvement in OS (HR 0.67, P=0.21, medians of 30 *versus* 23 months).⁵⁴ Secondly, in a cohort of 213 patients with mRCC treated with sunitinib, ASI users were reported to have a significantly improved OS (HR 0.40) and PFS (HR 0.55).¹¹ Finally, a larger study of mRCC patients treated with a range of VEGF-targeted therapies (sunitinib, sorafenib, axitinib, bevacizumab, temsirolimus and interferon- α ; 4736 patients included) found that ASI users have improved OS (HR 0.84, P=0.0105, 26.68 *versus* 18.7 months) compared to users of other anti-hypertensive agents, and that this association was not as prominent for patients treated with non VEGF-targeted agents.¹² The authors hypothesized that this may be related to the ability of ASIs to synergize with antiangiogenics to inhibit tumor cell proliferation and angiogenesis. Huillard *et al.* suggested that the action of ASI on muscle mass may result in less sarcopenia, a well-documented cause of overexposure and excessive toxicity to TKIs. Hence, the therapeutic index of VEGF-targeted therapies may be improved by ASI, resulting in subsequent longer duration of treatments, higher dose-intensity, and finally improved efficacy.⁵⁵ But in these analyses, there was no mention whether the patients under ASI had less early dose-limiting toxicities or less treatment interruptions. In contrast, a study of 1120 patients using a range of VEGF targeted therapies (sunitinib, sorafenib, pazopanib) across a number of indications (including mRCC) found no significant association (HR 0.92) between ASI use and OS.⁵⁶ Recently, Sorich *et al.* reported a secondary pooled analysis of two phase III randomized controlled trials (RCTs) of patients with mRCC: NCT00334282 comparing pazopanib to placebo and NCT00720941 comparing pazopanib to sunitinib.⁵⁷ Unlike the other studies, ASI users were defined as patients using an ASI only at baseline. Of 1545 patients pooled from the two RCTs, 649 (42%) were using one or more antihypertensive drugs at baseline, 385 (59%) of

which were using an ASI. In the multivariable analysis of patients using pazopanib or sunitinib, no significant association was observed between baseline ASI use and OS (HR 0.97, $P=0.80$) or PFS (HR 0.88, $P=0.17$). Exploratory subgroup analysis of NCT00720941 highlighted that the effect of baseline ASI use on OS may differ between patients treated with sunitinib and pazopanib. *Post hoc* subgroup analysis of the COMPARZ clinical trial highlighted that the relative efficacy of pazopanib and sunitinib may differ depending on background use of ASIs with results suggesting a greater benefit among sunitinib-treated patient using ASIs compared to pazopanib-treated patients.

Management of hypertension

The management of HTN has been individualized in terms of the HTN stage and other special situations (*i.e.*, coronary disease or heart failure) that may coexist with HTN.⁵⁸ However, all published guidelines for HTN management give no clear recommendations about cancer patients who suffer from HTN caused by antiangiogenic drugs. At the onset, HTN should be treated immediately, with standard hypertensive therapy based on the current guidelines of the European Society of HTN.⁵⁹ Specific guidelines consist of actively monitoring BP⁶⁰ throughout treatment with VEGF inhibitors, with more frequent assessments during the first cycle of treatment; this is because preexisting HTN should be identified and addressed before initiation of therapy⁶¹ to avoid serious vascular events. The optimal BP level should be less than 140/90 mmHg for most patients, but it should be set up on a case-by-case basis.⁶² The JCN7 guidelines proposed a lower level of BP (<130/90 mmHg) in high-risk patients, *i.e.*, those with diabetes, chronic kidney disease and coronary artery disease. In addition, regarding cancer patients who receive VEGFi agents, it has been suggested that antihypertensive treatment accompanied with dose modification of VEGFi or even a second antihypertensive regimen should be initiated when the BP reaches above 140/90 mmHg level or a 20 mmHg increase in diastolic BP above baseline.⁶³ Especially if the VEGFi-induced HTN is severe or persistent even after the administration of antihypertensive drugs or the individualized dose adaptation of VEGFi, temporarily or permanently stopping of antiangiogenic treatment may be required. Nevertheless, it has been observed that most cancer patients with VEGFi-induced HTN respond sufficiently to the standard schemes of antihypertensive treatment.⁶⁴ Antihypertensive therapies including ASI (ACE and ARB), or adrenoceptor blockers, calcium channel blockers (CCBs) as well as diuretics have been used as treatment of VEGFi-induced HTN. Optimal anti-hypertension medication has not yet been defined, and clinicians should consider individual patients' comorbid conditions when selecting classes of antihypertensive drugs for treatment. It is generally admitted that ACE and ARB are more effective in treating anti-VEGF-associated HTN, are better tolerated and have antiproteinuric effects, which may contribute to protection of renal function.^{65,66} CCBs may reduce microvascular rarefaction and improve angiogenesis but concerns have been raised over the safety of CCBs, particularly non-dihydropyridines, because they interfere with CYP3A4 activity.^{25,67,68} Due to the fact that VEGFi agents are metabolized by the cytochrome P450 and mainly by CYP3A4, non-dihydropyridines are likely to inhibit their metabolism leading to a dangerous increase of their plasma concentration. Because VEGF is known to increase endothelial NO, antihypertensives that increase endogenous NO (*e.g.*, nitrates, phosphodiesterase inhibitors, or the β -blocker nebivolol) might be of particular interest and merit evaluation in prospective clinical trials.^{69,70} Diuretics also have been used successfully to manage increases in BP arising from cancer treatment; however, thiazide-type diuretics should be used cautiously, particularly in patients prone to dehydration or hypercalcemia.^{71,72} Results from this literature review suggest that

further clinical studies are needed to identify optimal treatments for managing targeted therapy-related HTN.

Conclusions

The relationship between VEGF inhibitors and HTN is to day well established, and clinicians must recognize that these drugs may aggravate cardiac risk factors. Early introduction or even prophylactic use of antihypertensive drugs can allow maintenance of therapy despite the onset of HTN. Specific recommendations about ASI use in patients with mRCC receiving targeted therapy cannot be made on the results of the data reported on the increase of survival. Finally, no clear recommendation for an antihypertensive agent can be made in this context and further clinical collaborative research is necessary to direct both VEGFi anticancer treatment and management of its side effects such as HTN to a more personalized strategy.

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