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ORIGINAL RESEARCH

Hypertension among patients with renal cell carcinoma receiving axitinib or sorafenib: analysis from the randomized phase III AXIS trial

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Abstract Inhibitors of the vascular endothelial growth factor (VEGF) pathway frequently induce hypertension when used to treat patients with advanced renal cell carcinoma (RCC). This analysis characterizes hypertension and hypertension-related events in patients treated with the VEGF pathway inhibitors axitinib or sorafenib in the AXIS trial. AXIS was a randomized phase III study of axitinib versus sorafenib in patients with metastatic RCC following failure of one prior systemic regimen. Patients with uncontrolled hypertension were excluded, but patients with hypertension controlled with antihypertensive medication were allowed to participate. Guidelines for hypertension management included adjustment or addition of antihypertensive medications and/or axitinib or sorafenib dose reductions, interruptions, or discontinuations. Treatment-emergent all-causality hypertension occurred in 145 (40.4 %) axitinib-treated patients (N=359) and 103 (29.0 %) sorafenib-treated patients (N=355), with grade 3 hypertension reported in 55 (15.3 %) and 38 (10.7 %) patients, respectively, and grade 4 hypertension reported in one (0.3 %) patient in each arm. Hypertension-related events led to axitinib dose interruptions (n=46; 12.8 %), dose reductions (n=16; 4.5 %), or discontinuations (n=1; 0.3 %). Approximately 50 % of axitinib-treated patients with grade 3 or 4 hypertension continued treatment for ≥ 9 months. Hypertension-related sequelae occurred in <1 % of axitinib-treated patients. Hypertension was more frequently observed during treatment with axitinib than sorafenib in patients with RCC, but axitinib-induced hypertension rarely led to treatment discontinuation or cardiovascular sequelae. Recommendations for monitoring blood pressure and managing hypertension during axitinib therapy are presented.

Keywords Renal cell carcinoma · Axitinib · Sorafenib · Hypertension · Blood pressure

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Introduction

Axitinib is a tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptors 1–3 [1]. The phase III AXIS trial was conducted to compare progression-free survival (PFS) in patients with metastatic renal cell carcinoma (RCC) treated with axitinib versus sorafenib, an active comparator, following failure of one prior systemic regimen [2]. Median PFS was 6.7 months with axitinib versus 4.7 months with sorafenib (hazard ratio = 0.665; one-sided p<0.0001).

Occurrence of hypertension with use of VEGF pathway inhibitors has been well documented [3–7]. All-grade hypertension, ranging from 17 to 40 %, has been reported in studies of axitinib, bevacizumab/interferon-alpha, sunitinib, sorafenib, and pazopanib in patients with RCC [2, 8–11]. Although the

exact mechanism by which VEGF pathway inhibitors induce hypertension has not been determined definitively, two key hypotheses have been generated. Firstly, acute inhibition of VEGF signaling can lead to disruption of vasodilator production and subsequent arteriolar vasoconstriction. Studies have pointed to a VEGF pathway inhibitor-induced decrease in nitric oxide synthase and nitric oxide production that can result in vasoconstriction and increased blood pressure (BP) [1, 12–14]. Secondly, a decrease in the number of microvascular endothelial cells and subsequent depletion of normal microvessel density (rarefaction) occurs upon VEGF signaling inhibition [14–17].

Hypertension associated with VEGF pathway inhibitors is often observed in the context of preexisting hypertension. The Centers for Disease Control and Prevention reported the incidence of hypertension from 2005 to 2008 in the US general population, ages 45–64 years, was 40.6 % (95 % confidence interval [CI], 38.1–43.2) [18]. For those aged ≥65 years, the incidence was 70.3 % (95 % CI, 67.5–73.2). Furthermore, an epidemiologic study of 1,136 patients with RCC reported hypertension as a comorbid condition in 58 % of patients at the time of diagnosis [19].

In the AXIS study, hypertension was the second-most common adverse event (AE) in the axitinib arm, occurring in 40 % of patients, and was more frequently reported in axitinib-treated versus sorafenib-treated patients (29 %) [2]. Herein, hypertension and its management strategies in the AXIS trial are described, with a focus on axitinib treatment.

Patients and methods

Patients

As described elsewhere [2], eligible patients had histologically or cytologically confirmed RCC with clear-cell component, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 [20], and RECIST-defined progressive disease, as assessed by investigators, after one prior sunitinib-, bevacizumab/interferon-alpha-, temsirolimus-, or cytokine-based regimen. Patients were required to have no evidence of preexisting uncontrolled hypertension (BP >140/90 mm Hg) as determined by two baseline BP readings taken ≥1 h apart. Patients with BP controlled by antihypertensive therapy were eligible.

The trial was approved by the institutional review board or ethics committee at each center and complied with Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. All patients provided written informed consent. AXIS is registered on ClinicalTrials.gov (NCT00678392).

Procedures

Details of study design and statistical methods have been reported [2]. Patients were stratified according to Eastern Cooperative Oncology Group performance status (ECOG PS) and type of prior treatment and then randomized 1:1 to axitinib or sorafenib. The primary endpoint was PFS based on independent radiology review committee assessment.

Axitinib was administered orally at a starting dose of 5 mg twice daily. Sorafenib was administered orally at a starting dose of 400 mg twice daily. Dose modifications of axitinib and sorafenib were previously described [2, 21]. Patients were treated until disease progression, occurrence of unacceptable toxicity, death, or withdrawal of consent.

Assessment of medical history, physical examination, vital signs, clinical laboratory evaluation, and ECOG PS were performed at baseline, week 2, week 4, and every 4 weeks thereafter [2]. Safety was assessed throughout the study. Severity of AEs was graded according to Common Terminology Criteria for Adverse Events (CTCAE) 3.0 [22].

Management of hypertension

Patients were issued oscillometric BP cuffs and instructed to measure BP at home twice daily prior to taking study drug. All measurements were to be taken in a seated position after resting for 5 min and recorded in a diary. Patients were instructed to contact their physicians immediately if systolic BP was >150 mmHg, diastolic BP was >100 mmHg, or if they developed symptoms perceived to be related to elevated BP (e.g., headache, visual disturbance).

Hypertension management guidelines for patients receiving axitinib (Table 1) were based on two BP readings, preferably taken in-clinic and separated by ≥1 h. Patients receiving antihypertensive medications who had axitinib withheld were instructed to monitor closely for hypotension. Due to the short plasma half-life of axitinib (2.5–6.1 h) [23], BP was expected to decrease within 1–2 days following dose interruption.

In patients receiving sorafenib, temporary or permanent discontinuation of drug was to be considered in cases of severe or persistent hypertension despite administration of antihypertensive medications.

Statistical analysis

Analyses were conducted in the safety population (patients who received at least one dose of study drug).

Results

Patients

Of 723 enrolled patients, 361 were randomized to axitinib and 362 to sorafenib; 359 and 355 patients, respectively, were included in the safety population. Baseline characteristics were similar between treatment arms [2]. In axitinib and

Table 1 Guidance on axitinib dose interruption and reduction for hypertension in the AXIS trial

Degree of BP elevation			
Systolic		Diastolic	Management
Two readings separated by ≥1 h showing >150 mmHg	OR	Two readings separated by ≥1 h showing >100 mmHg	If not on maximal antihypertensive treatment, institute new or additional antihypertensive medication and maintain axitinib dose. If on maximal antihypertensive treatment, reduce to one lower dose level
Two readings separated by ≥1 h showing >160 mmHg	OR	Two readings separated by ≥1 h showing >105 mmHg	Interrupt dosing; adjust antihypertensive medication; as soon as BP <150/100 mmHg, restart axitinib at one lower dose level
Recurrent >150 mmHg (two readings separated by ≥1 h) following previous dose reduction	OR	Recurrent >100 mmHg (two readings separated by ≥1 h) following previous dose reduction	Repeat axitinib dose reduction by one lower dose level

BP blood pressure

sorafenib arms, respectively, 164 (45.4 %) and 189 (52.2 %) patients had a medical history of hypertension and 167 (46.5 %) and 171 (48.2 %) were receiving antihypertensive medication prior to the start of study treatment (Table 2).

Incidence of hypertension

Treatment-emergent, all-causality hypertension was reported in 145 (40.4 %) patients receiving axitinib and 103 (29.0 %) patients receiving sorafenib (Table 3), of which 141 (97.2 %) and 103 (100 %) patients, respectively, had treatment-related hypertension per the investigator. Grade 3 hypertension was reported in 55 (15.3 %) patients receiving axitinib and 38 (10.7 %) patients receiving sorafenib. One (0.3 %) patient in each arm experienced grade 4 hypertension. No fatal (grade 5) hypertension events were reported.

Hypertensive crisis (defined as a potentially life-threatening increase in BP) was reported in none of the sorafenib-treated patients and in two (0.6 %) axitinib-treated patients. The first patient had a prior history of thrombosis and baseline BP of 120/80 mmHg. After 2 weeks of treatment with axitinib 5 mg twice daily, this patient's highest home BP reading was 142/91 mmHg, and clonidine was given for 2 weeks and then discontinued. A few days later, a home BP reading reached a maximum of 193/122 mmHg. Axitinib was withheld temporarily, and treatment with irbesartan/hydrochlorothiazide (150/12.5 mg) was initiated. The patient subsequently restarted axitinib and had ongoing grade 1 hypertension. The patient continued axitinib at 5 mg twice daily and completed 5.8 months of axitinib treatment as of the data cutoff date.

The second axitinib-treated patient had a history of coronary artery disease and was treated with axitinib 5 mg twice

Table 2 Antihypertensive medication use

Concomitant antihypertensive medication[a]	Axitinib (*N*=359) *n* (%)	Sorafenib (*N*=355) *n* (%)
Before first dose of axitinib		
Receiving antihypertensive medication	167 (46.5)	171 (48.2)
Amlodipine or amlodipine besylate (calcium channel blocker)	54 (15.0)	47 (13.2)
Atenolol (β1-receptor antagonist)	20 (5.6)	14 (3.9)
Hydrochlorothiazide (diuretic)	18 (5.0)	16 (4.5)
Lisinopril (ACE inhibitor)	16 (4.5)	25 (7.0)
Ramipril (ACE inhibitor)	22 (6.1)	10 (2.8)
On-study		
Started antihypertensive medication or increased dose of existing antihypertensive medication	196 (54.6)	141 (39.7)
Amlodipine or amlodipine besylate (calcium channel blocker)	88 (24.5)	61 (17.2)
Atenolol (β1-receptor antagonist)	18 (5.0)	8 (2.3)
Hydrochlorothiazide (diuretic)	19 (5.3)	13 (3.7)
Lisinopril (ACE inhibitor)	27 (7.5)	14 (3.9)

ACE angiotensin-converting enzyme

[a] Administered to ≥5 % of patients

Table 3 All-causality hypertension-related adverse events

Preferred term[a]	Axitinib (*N*=359) *n* (%)		Sorafenib (*N*=355) *n* (%)	
	All grades	Grade 3/4[b]	All grades	Grade 3/4[b]
Hypertension[c]	145 (40.4)	56 (15.6)	103 (29.0)	39 (11.0)
BP increased	3 (0.8)	1 (0.3)	3 (0.8)	2 (0.6)
Hypertensive crisis	2 (0.6)	2 (0.6)	0	0
Accelerated hypertension[d]	1 (0.3)	1 (0.3)	0	0

BP blood pressure, *CTCAE* Common Terminology Criteria for Adverse Events

[a] Medical Dictionary for Regulatory Activities (MedDRA), v.13.1

[b] No grade 5 all-causality hypertension-related events were reported

[c] Per CTCAE v3.0 [22]; grade 1 hypertension—asymptomatic, transient (<24 h) increase in BP to >150/100 mmHg or in diastolic BP by >20 mmHg with intervention not indicated; grade 2 hypertension—recurring or persistent (≥24 h) increase in BP to >150/100 mmHg or in diastolic BP by >20 mmHg with monotherapy possibly indicated; grade 3 hypertension—requiring more than one drug or more intensive therapy; and grade 4 hypertension—BP increases with life-threatening consequences

[d] Progressive hypertension with the funduscopic vascular changes of malignant hypertension but without papilledema

daily with an increase to 7 mg twice daily at week 2 of treatment. At month 4 of treatment, the patient experienced hypertensive crisis with BP 180/100 mmHg and was treated at a local hospital. Axitinib was withheld, and the event resolved within 10 days. Axitinib was restarted at 5 mg twice daily, and the patient completed 8.3 months of treatment as of the data cutoff date. No other cardiovascular toxicities were reported for either patient while on study.

Onset of hypertension

Median time to onset of grades 1–2 hypertension in the axitinib versus sorafenib arms was 16 versus 13 days, whereas median time to onset of grade ≥3 hypertension was 24 versus 9 days.

When grouped according to baseline antihypertensive medication use versus non-use, median time to onset of grade ≥3 events was 15 versus 29 days, respectively, in the axitinib arm (Table 4). In sorafenib-treated patients, median time to onset of grade ≥3 hypertension was similar in both subgroups.

Hypertension-related medical history, hypertension sequelae, and clinical management of hypertension in axitinib-treated patients

Hypertension-related medical history recorded for axitinib-treated patients included angina pectoris (*n*=4), cerebrovascular accident (*n*=2), myocardial infarction (*n*=6), myocardial ischemia (*n*=8), and transient ischemic attack (*n*=2). Of these patients, seven reported an AE of hypertension on study but none experienced additional cardiovascular events.

Rates of individual hypertension-related sequelae were generally low (<1 %) in axitinib-treated patients (Table 5). In seven of nine patients who experienced hypertension-related sequelae, hypertension within the first 8 weeks of treatment was reported either as an AE or as elevated BP, based on in-clinic or home monitoring. One of the two remaining patients had an increased home BP reading within the first 8 weeks of treatment from 120/80 to 140/90 mmHg 1 day after discontinuing amlodipine.

Based on in-home and in-clinic BP monitoring, hypertension events were managed by treatment with antihypertensive medication (Table 2) and by axitinib dose interruptions (12.8 %), dose reductions (4.5 %), and/or discontinuation (0.3 %). Of 56 axitinib-treated patients who experienced grade ≥3 hypertension, 30 (53.6 %) continued axitinib treatment for ≥9 months.

Nineteen (5.3 %) axitinib-treated patients experienced hypotension while on study; of these, hypertension, accelerated hypertension, or increased BP was reported in eight (42.1 %) patients. In the majority of cases, hypotension was considered to have resulted from axitinib dose modification or interruption and/or administration of antihypertensive therapy. A serious AE of hypotension requiring hospitalization was reported in one axitinib-treated patient and associated with volume depletion, nausea, vomiting, acute renal failure, and prerenal azotemia; the event was considered by the investigator to be unrelated to axitinib treatment.

Blood pressure trends during axitinib treatment

In patients receiving axitinib, median values for maximum and last on-treatment in-clinic BP readings were higher than for baseline readings, but returned to baseline after axitinib discontinuation. Similar trends were observed using change in diastolic BP from baseline (Table 6).

Table 4 Time to onset of hypertension event according to antihypertensive medication use at baseline

	Axitinib (*N*=359)		Sorafenib (*N*=355)	
Time to onset of hypertension event[a]	No antihypertensive medication (*n*=192)	Antihypertensive medication (*n*=167)	No antihypertensive medication (*n*=184)	Antihypertensive medication (*n*=171)
Any grade, *n* (%)	87 (45.3)	62 (37.1)	56 (30.4)	50 (29.2)
Median, days (range)	15 (1–371)	15 (1–199)	13 (1–368)	8 (1–367)
Grade ≥3, *n* (%)	26 (13.5)	33 (19.8)	11 (6.0)	30 (17.5)
Median, days (range)	29 (1–165)	15 (1–199)	9.0 (1–267)	9.5 (3–467)

[a] Included all-causality, treatment-emergent adverse events reported as accelerated hypertension, blood pressure increase, hypertension, or hypertensive crisis

Discussion

Although hypertension was the second-most commonly reported treatment-emergent AE in the axitinib arm and more frequently reported in patients treated with axitinib versus sorafenib [2], the incidence of potential hypertension-related sequelae was low with axitinib. There was a slightly higher incidence of hypertension, proteinuria, and hypothyroidism in those patients who did not have their axitinib dose increased (≤5 mg twice daily throughout the study; data not shown). These results should be interpreted with caution since patients were not prospectively randomized to receive an increase in dose above the twice-daily 5 mg starting dose or not, and dose increases were specified in the protocol based on individual patient tolerability. As previously reported, hypertension occurred as early as day 1 of treatment with axitinib [24] or sorafenib [25]. Median time to onset of all-grade hypertension was independent of baseline antihypertensive use; however, in the axitinib arm, time to onset of grade ≥3 hypertension was nearly twice as long in patients not receiving antihypertensive medications at baseline. This may reflect closer monitoring of patients receiving antihypertensive therapy at baseline, according to standard of care, leading to a tendency toward an earlier reporting of grade ≥3 hypertension. Alternatively, patients already receiving antihypertensive medication may have been more biologically susceptible to earlier axitinib-induced hypertension.

In the AXIS trial, the severity of hypertension was graded according to CTCAE 3.0 [22]. The definition of hypertension in this version does not include patients with BP 140–150/90–100 mmHg and has overlapping definitions of grade 2 and 3 hypertension, which may be inconsistently applied by clinicians in grading hypertension. The most recent version of CTCAE, version 4.0 [26], was updated subsequent to trial initiation and includes hypertension grading definitions similar to recommendations from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [27], i.e., inclusion of BP ≥140/90 mmHg in

Table 5 Incidence of potential hypertension-related sequelae in axitinib-treated patients

	Axitinib (*N*=359) *n* (%)			Baseline features of individual patients		
Preferred term[a]	All grades	Grade 3/4	Grade 5	Medical history	BP[b] (mmHg)	Antihypertensive medication use[c]
TIA	3 (0.8)	3 (0.8)	0	Arterial hypertension	120/80	No
				High cholesterol	120/80	No
				Diabetes	127/74	Yes
Hypertensive crisis	2 (0.6)	2 (0.6)	0	CHD	130/85	NA
				Thrombosis	110/70	No
Angina pectoris	1 (0.3)	0	0	Diabetes	115/75	No
Cerebral hemorrhage	1 (0.3)	1 (0.3)	0	TIA	129/82	No
Cerebrovascular accident	1 (0.3)	0	1 (0.3)	None	100/60	Yes
Leukoencephalopathy[d]	1 (0.3)	1 (0.3)	0	Atrial fibrillation	115/62	No

BP blood pressure, *TIA* transient ischemic attack, *CHD* coronary heart disease, *NA* not available

[a] Medical Dictionary for Regulatory Activities (MedDRA), v.13.1

[b] Blood pressure at screening visit

[c] Antihypertensive medication use on cycle 1 day 1 of axitinib treatment

[d] Reports of reversible posterior leukoencephalopathy syndrome were reported as leukoencephalopathy

Table 6 Trends in blood pressure measurements over the course of axitinib treatment

	No.	Minimum	10th percentile	Median	90th percentile	Maximum
sBP (mmHg)						
Baseline	359	85	109.0	125.0	140.0	176
Maximum on treatment	352	95	127.5	143.0	162.0	195
Last on treatment	352	81	108.0	127.5	145.0	175
At follow-up[a]	118	77	100.0	120.5	140.0	155
dBP (mmHg)						
Baseline	359	47	64.5	77.0	87.5	100
Maximum on treatment	352	63	80.0	90.0	103.0	123
Last on treatment	352	55	68.5	80.0	92.0	108
At follow-up[a]	118	40	60.0	75.5	90.0	101
ΔdBP (mmHg)						
Maximum on treatment	352	−18	2.5	14.0	27.0	43
Last on treatment	352	−34	−10.0	4.0	17.5	40
At follow-up[a]	118	−40	−13.5	1.3	15.0	30

sBP systolic blood pressure, *dBP* diastolic blood pressure, *ΔdBP* change in diastolic blood pressure from baseline

[a] Nearest blood pressure measurement after last day of treatment

the definition of grade 2 hypertension. Future application of standardized, less ambiguous definitions and grading of hypertension will help identify and treat patients who develop hypertension while receiving VEGF-targeting drugs.

The low incidence of hypertensive crisis and hypertension-related sequelae, and the 27- and 25-day median duration of hypertension (data not shown) in the axitinib and sorafenib arms, respectively, suggest that AXIS trial guidelines for managing hypertension were effective. However, managing hypertension may be more challenging among patients receiving VEGF pathway inhibitors in non-trial settings, wherein patients are not required to meet strict eligibility criteria for a clinical study. Management of hypertension in patients with RCC receiving sorafenib has been reported elsewhere [28–30]. Based on clinical experience and available data from the AXIS trial, we recommend clinicians, in collaboration with their patients and other practitioners, establish a strategy to monitor BP throughout the course of axitinib therapy and actively manage treatment-induced hypertension.

Prior to axitinib treatment, the clinician should assess the patient's BP status, antihypertensive medication use, and cardiovascular risk factors (Fig. 1). Using past and present BP measurements, patients may be classified as normotensive, uncontrolled hypertensive, medication-controlled hypertensive, or sub-optimally medication-controlled hypertensive. Patients with uncontrolled hypertension may be treated with short-acting antihypertensive agents for rapid titration and, once stable, switched to long-acting agents before initiating axitinib. In those with sub-optimally controlled hypertension, the dose of current medication may be increased or new medication(s) added. Pretreatment evaluation of risk factors for cardiovascular disease, e.g., cardiac conditions, peripheral vascular disease, renal disease, or diabetes mellitus, is essential since patients with one or more risk factors may require closer monitoring during axitinib therapy. Likewise, other preexisting conditions that may be associated with BP increases, e.g., arterial thromboembolism, diabetes, or cardiac conditions, should be aggressively managed. The clinician should be aware if the patient is receiving hypertension-inducing agents, e.g., steroids or hormones, which may complicate management if axitinib-induced hypertension develops.

Pretreatment patient education about the importance of BP assessments, including home monitoring, and the likelihood of developing hypertension during therapy is critical for empowering the patient and improving compliance. The clinician should assist in calibrating the home BP-monitoring device, train the patient in its proper use (additional details below), and discuss recording and reporting of BP measurements.

During axitinib therapy, BP should be monitored regularly in-clinic and at home (Fig. 1). In-clinic and home BP should be measured with the patient in a seated position and after resting for 5 min. In-clinic measurements should be recorded as the mean of at least two measurements taken 3 min apart, and clinicians should evaluate for white-coat hypertension [31]. In the AXIS trial [2], in-clinic BP measurements were performed at baseline, week 2, week 4, and every 4 weeks thereafter. Clinical trial protocols from the National Cancer Institute recommend in-clinic BP monitoring every week during the first cycle of therapy with a VEGF pathway inhibitor (for 4 weeks with axitinib) and then every 2–3 weeks during treatment [32]. For home BP monitoring, patients should measure BP prior to axitinib dosing and avoid exercise,

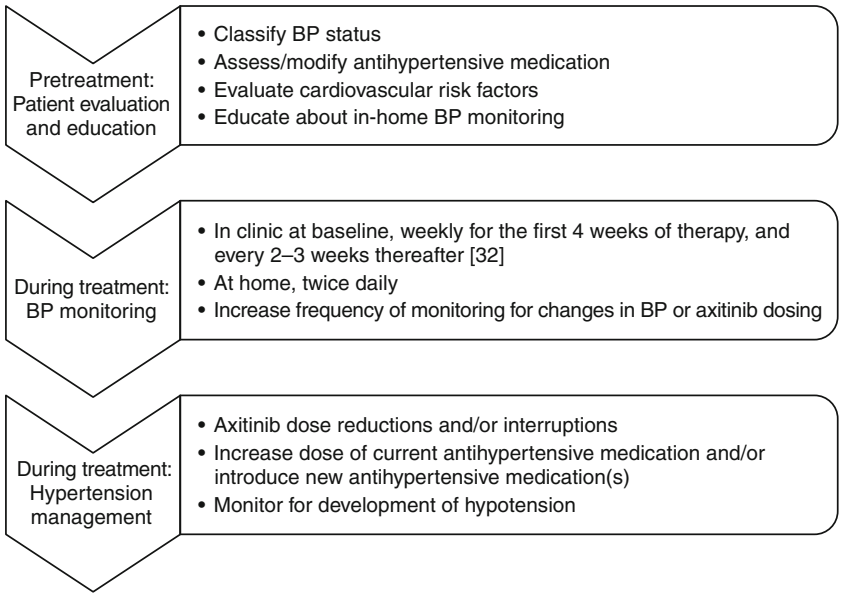

Fig. 1 Guidance on monitoring and managing hypertension in patients with renal cell carcinoma treated with axitinib. *BP* blood pressure

caffeine, and tobacco for at least 30 min prior. Initially, patients should measure BP twice daily, per AXIS guidelines [2]; however, home BP monitoring may be relaxed to once daily after 8 weeks of treatment if BP is controlled and the axitinib dose has not been modified. All home BP readings should be recorded in a diary and brought to clinic visits. Frequency of in-clinic and home monitoring may be increased if BP elevations are observed or if the axitinib dose is modified.

If hypertension develops during therapy, the axitinib dose should be reduced or interrupted per AXIS trial recommendations (Table 1, Fig. 1) and axitinib prescribing information [23]. Additionally, the dose of current antihypertensive therapy may be increased and/or additional antihypertensive medications introduced. Potential drug–drug interactions between axitinib and antihypertensive medications should be considered before administration in combination. In vitro studies have shown that axitinib is primarily metabolized by cytochrome P450 (CYP) 3A4/5 and, to a lesser extent, by CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase 1A1 [23], and therefore unlikely to have drug–drug interactions with commonly used antihypertensive agents belonging to the class of angiotensin-converting enzyme inhibitors, including angiotensin II receptor blockers (enalapril, captopril, losartan, vasartan), beta-blockers (atenolol, metoprolol, labetalol), or diuretics (hydrochlorothiazide). Within the class of calcium channel blockers, moderate CYP3A4/5 inhibitors (e.g., verapamil, diltiazem) were not recommended during the AXIS trial. Other calcium channel blockers (e.g., amlodipine, bepridil, felodipine) were less likely to raise axitinib plasma levels and were allowed during the study. The choice and dosage of antihypertensive medication should be considered in the context of the patient's general medical condition and health status, in accordance with current standard of care and local guidelines. Exercise and dietary control, if possible, should be included in recommendations for managing hypertension. Clinicians must monitor for hypotension in patients receiving antihypertensive medications who have their axitinib dose interrupted [23]. Patients who were previously normotensive may be more likely to experience rapid BP decreases than those with prior hypertension (M. Baum, personal communication) and may require more rigorous monitoring for a few days after axitinib interruption.

Inhibitors of the VEGF pathway are rarely curative and as a result, patients may need to be treated with these agents for extended duration to control their disease. With potential for RCC to become a chronic disease, management of therapy-induced BP changes is critical, and the clinician's goal should be controlling hypertension throughout treatment of the primary disease. Proper BP monitoring and management would be expected to reduce hypertension-related sequelae and may allow patients to remain on treatment for longer periods [33]. The analyses presented here, and resulting recommendations, are limited by retrospective analyses and the lack of data for patient compliance. Observational studies in much larger populations of patients with RCC treated with axitinib will be needed to evaluate hypertension and related sequelae in the real-world clinical experience.

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