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ORIGINAL ARTICLE
Hypertension and Circulatory Control

Axitinib Induces and Aggravates Hypertension Regardless of Prior Treatment With Tyrosine Kinase Inhibitors

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Background: Axitinib is a tyrosine kinase inhibitor (TKI) that inhibits vascular endothelial growth factor receptor signaling and is approved for second-line treatment of advanced renal cell carcinoma (RCC). Although the occurrence of hypertension with axitinib use has been documented, it is unclear whether a first-line TKI regimen can significantly affect the development of hypertension when axitinib is used as second-line therapy.

Methods and Results: In this single-center retrospective study, advanced RCC patients treated with axitinib after first-line chemotherapy were divided into 2 groups according to the use of TKIs as part of first-line treatment before the initiation of axitinib. Clinical outcomes were compared between patients who were treated with (TKI(+); n=11) or without (TKI(–); n=11) a TKI. Although 63.6% of all patients had hypertension at baseline, axitinib-induced hypertension developed in 81.8% of patients, and 36.4% of patients experienced Grade 3 hypertension. After initiation of axitinib, both systolic and diastolic blood pressures and the hypertension grade were significantly elevated both in the TKI(+) and TKI(–) groups, and the number of antihypertensive drugs was significantly increased among all patients.

Conclusions: This study suggests the need for proper monitoring and management of blood pressure in RCC patients treated with axitinib, regardless of a prior regimen with or without TKIs.

Key Words: Axitinib; Hypertension; Renal cell carcinoma; Tyrosine kinase inhibitor; Vascular endothelial growth factor receptor

Hypertension is a comorbid condition that frequently occurs in cancer patients, as well as in individuals without cancer, with cancer registries demonstrating that the coexistence of hypertension affects prognosis.[1–3] Hypertension can be caused or worsened by some types of cancers, such as renal cell carcinoma (RCC),[4] and, more importantly, by adverse effects of chemotherapeutic drugs, such as anti-angiogenic vascular endothelial growth factor (VEGF) signaling pathway (VSP) inhibitors.[2,3] In cancer patients treated with VSP inhibitors, the incidence of hypertension ranges from 30% to 80%, depending on patient characteristics (i.e., age, prior hypertension, comorbid cardiovascular and metabolic diseases), cancer type, and drug types and protocols.[5] According to the Stanford Cancer Institute database, the frequency and severity of cardiovascular toxicities are high in metastatic RCC patients treated with VSP inhibitors, with 48% of bevacizumab-treated patients, 59% of sorafenib-treated patients, and 52% of sunitinib-treated patients developing hypertension.[6] Indeed, VSP inhibitors have substantially improved the rates of response and overall survival (OS) in advanced RCC patients, and several VSP inhibitors (pazopanib, axitinib, cabozantinib, and lenvatinib), in addition to sorafenib and sunitinib, have been approved by the US Food and Drug Administration (FDA).[4,7] Under such circumstances, clinicians need to understand the drug-specific effects of individual VSP inhibitors on blood pressure, and appropriately manage blood pressure to avoid interruptions to effective anti-angiogenic therapy and to achieve long-term reductions in cardiovascular risks for patients with a prolonged life expectancy.

Axitinib is a potent tyrosine kinase inhibitor (TKI) that selectively inhibits VEGF receptor (VEGFR)-1, -2, and -3.[8,9] Axitinib has been approved for the treatment of

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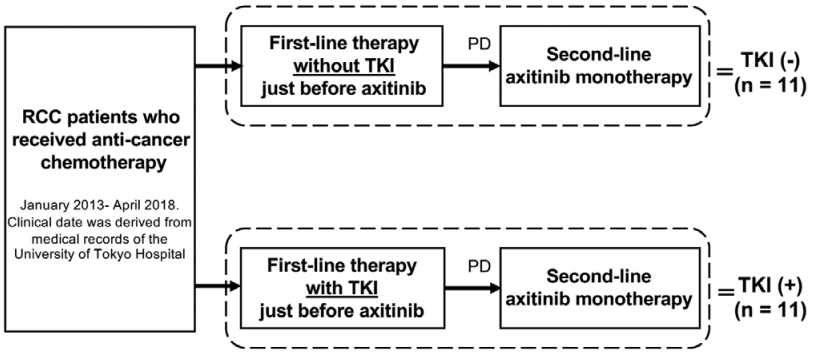

Figure 1. Study profile. PD, progressive disease; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.

advanced RCC as a second-line drug. In a randomized Phase 3 trial (AXIS), axitinib significantly improved median progression-free survival (mPFS) and OS compared with sorafenib in 723 patients with refractory RCC who had disease progression despite first-line therapy.[10,11] Furthermore, in recent studies, combination therapies using axitinib plus immune checkpoint inhibitors (pembrolizumab or avelumab) resulted in significantly longer mPFS and OS in advanced RCC patients than conventional chemotherapy.[12,13] In addition, some currently ongoing studies are investigating expanded clinical indications for axitinib in solid malignancies such as advanced melanoma and sarcoma.[14,15] Because of the increase in the number of RCC survivors and the increased indications for axitinib, familiarity with adverse cardiovascular events in relation to axitinib will become more important for cardiologists as well as for oncologists.

The reported incidence of axitinib-induced hypertension varies from 18% to 59% depending on the baseline characteristics of the patients enrolled in the different studies.[10,16–19] In particular, treatment choices for first-line therapy can have a significant effect on the development of hypertension when axitinib is used as second-line therapy. First-line options include TKIs such as sunitinib and pazopanib, and bevacizumab plus interferon (IFN)-α, as well as mammalian target of rapamycin (mTOR) inhibitors and high-dose interleukin-2.[4,7] It was hypothesized that the effect of axitinib on blood pressure may differ between patients who had received TKIs as part of first-line therapy and those who had not. In this study, we investigated the effect of prior TKI treatment as part of first-line therapy on axitinib-induced hypertension as a second-line treatment.

Methods

Study Design

A single-center retrospective study was performed by collecting clinical data from electronic medical records of patients with advanced RCC treated with axitinib after first-line systemic chemotherapy in The University of Tokyo Hospital between January 2013 and April 2018. This study complied with the Declaration of Helsinki, and was approved by the Research Ethics Committee, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (Reference no. 2020222NI).

Clinical parameters and outcomes were compared between patients who were (TKI(+)) or were not (TKI(−)) treated with TKIs as part of the first-line therapy just before initiation of axitinib treatment. The major outcomes of interest were the hypertension grade and changes in the number of antihypertensive drugs being used. Adverse effects were assessed in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[20] Blood pressures were measured in patients in a seated position after 5 min rest in the morning at each hospital visit. Hypertension at baseline was defined as systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg, a past history of hypertension, or the use of antihypertensive drugs. After initiation of axitinib, hypertension was defined as SBP >140 mmHg or DBP >90 mmHg at each hospital visit. Advanced RCC was defined as Stage IV or locally recurrent, unresectable disease. Progressive disease (PD) was defined as radiological tumor enlargement acquired by appropriate imaging, according to Response to Evaluation Criteria In Solid Tumor (RECIST) version 1.1.[21]

Axitinib was prescribed according to the conventional regimen at a dose of 5 mg b.i.d., increased to 7 or 10 mg b.i.d. continuously unless patients had PD or unbearable adverse events. Depending on the severity of adverse effects, the dose of axitinib was reduced to 3 or 2 mg b.i.d., or terminated altogether.

Statistical Analysis

Clinical data are expressed as the mean±SD. Data were compared between the 2 groups using Wilcoxon's rank-sum test. Two-sided $P<0.05$ was considered significant. All statistical analyses were performed using JMP® 14 (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics at Baseline

The study profile is shown schematically in **Figure 1**. Twenty-two advanced RCC patients who were treated with axitinib as part of second-line systemic chemotherapy at The University of Tokyo Hospital between January 2013 and April 2018 were screened at baseline. Baseline patient characteristics are summarized in **Table 1**. The mean age at the initiation of axitinib was 63.3 years, and 77.3% of patients in the study population were male. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. In both the TKI(+) and TKI(−)groups (n=11 in each group), 63.6% of patients

Table 1. Baseline Patient Characteristics

	All patients	TKI(−)	TKI(+)	P value
No. patients	22	11	11	NS
Age (years)	63.3±13.6	63.8±10.1	62.8±16.5	NS
Male	17 (77.3)	9 (81.8)	8 (72.7)	NS
BMI (kg/m^2)	22.2±4.0	22.2±4.5	22.3±3.6	NS
Hypertension	14 (63.6)	7 (63.6)	7 (63.6)	NS
SBP (mmHg)	115.4±10.3	113.9±11.4	116.9±8.9	NS
DBP (mmHg)	65.6±10.2	67.0±10.7	64.2±9.6	NS
Diabetes	3 (13.6)	3 (27.2)	0	NS
Current/former smoker	15 (68.2)	7 (63.6)	8 (72.7)	NS
Dyslipidemia	3 (13.6)	2 (18.2)	1 (9.1)	NS
Serum creatinine (mg/dL)	1.27±0.3	1.01±0.3	1.51±0.67	0.02
Cardiovascular disease	4 (18.2)	2 (18.2)	2 (18.2)	NS
Coronary artery disease	2 (9.1)	1 (9.1)	1 (9.1)	NS
Atrial fibrillation	1 (4.5)	1 (9.1)	0	NS
Chronic heart failure	1 (4.5)	0	1 (9.1)	NS
ECOG performance status				
0	14 (63.6)	7 (63.6)	7 (63.6)	NS
1	8 (36.4)	4 (36.4)	4 (36.4)	NS
>1	0	0	0	NS
Histological subtypes				
Clear cell	20 (90.9)	10 (90.9)	10 (90.9)	NS
Papillary	2 (9.1)	1 (9.1)	1 (9.1)	NS
Chemotherapy				
Interferon-α	2 (9.1)	2 (18.2)	0	NS
Everolimus	6 (27.3)	6 (54.5)	0	0.006
Sorafenib	1 (4.5)	0	1 (9.1)	NS
Sunitinib	9 (40.9)	0	9 (81.8)	0.002
Pazopanib	1 (4.5)	0	1 (9.1)	NS
Nivolumab	3 (13.6)	3 (27.2)	0	NS
Antihypertensive drugs				
ACEI/ARB	5 (22.7)	3 (27.2)	2 (18.2)	NS
Ca^{2+} channel blocker	7 (31.8)	2 (18.2)	5 (45.4)	NS
β-blocker	5 (22.7)	3 (27.2)	2 (18.2)	NS
Diuretics	5 (22.7)	3 (27.2)	2 (18.2)	NS

Unless indicated otherwise, data are presented as the mean±SD or as n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; ECOG, Eastern Cooperative Oncology Group; SBP, systolic blood pressure; TKI, tyrosine kinase inhibitor.

(n=7 in each group) had hypertension. Serum creatinine concentrations were significantly higher in the TKI(+) than TKI(−) group, probably because TKIs were preferably used in patients with renal dysfunction, whereas IFN-α or mTOR inhibitors (everolimus and temsirolimus) were avoided because of their renal toxicity.

Axitinib-Induced Hypertension

Changes in SBP and DBP after the initiation of axitinib are shown in **Figure 2**. Axitinib significantly increase blood pressure in all patients (SBP from 115.4±10.3 to 144.4±18.8 mmHg [P<0.001]; DBP from 65.6±10.2 to 82±14.2 mmHg [P<0.01]; **Figure 2A**). Furthermore, axitinib significantly elevated blood pressures in the TKI(−) group (SBP from 113.9±11.4 to 148.6±17.9 mmHg [P<0.001]; DBP from 67.0±10.7 to 83.5±15.2 mmHg [P<0.05]; **Figure 2B**) and TKI(+) groups (SBP from 116.9±8.to 140.2±18.7 mmHg [P<0.01]; DBP from 64.2±9.6 to 80.0±12.5 mmHg [P<0.05]; **Figure 2C**) separately.

Axitinib-induced hypertension developed in 81.8% of patients (n=18), and 36.4% of patients (n=8) experienced Grade 3 hypertension in both groups (**Table 2**). Grade 4 or 5 hypertension was not observed in the present study. Elevation of blood pressure occurred a few days after the initiation of axitinib, and 72.7% of patients were hospitalized when treatment with axitinib was initiated. The CTCAE grades of hypertension before and after the initiation of axitinib are shown in **Figure 3**. After initiation of axitinib, the grade of hypertension was significantly elevated in all patients (from 0.6±0.7 to 1.6±1.1; P<0.001; **Figure 3A**). Interestingly, a significant elevation in the hypertension grade was observed in the TKI(+) group (from 0.9±0.7 to 2.0±1.1; P=0.002; **Figure 3C**) and in the TKI(−) group (from 0.2±0.4 to 1.2±0.9; P=0.003; **Figure 3B**).

Axitinib-Induced Adverse Events Other Than Hypertension

The adverse events, other than hypertension, reported after initiation of axitinib are summarized in **Table 2**. Diarrhea

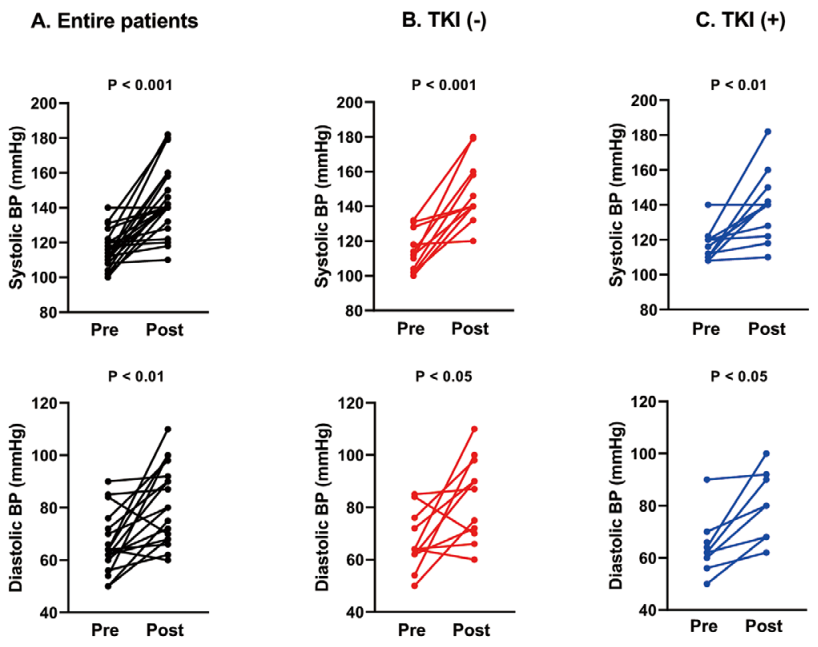

Figure 2. Changes in systolic (**Upper panels**) and diastolic (**Lower panels**) blood pressure in individual patients after the initiation of axitinib in all patients (**A**) and in patients who did not (**B**) or did (**C**) receive a tyrosine kinase inhibitor (TKI) as part of the first-line treatment regimen.

Table 2. Adverse Events After Initiation of Axitinib

	All patients (n=22)		TKI(–) (n=11)		TKI(+) (n=11)	
	All grades	≥Grade 3	All grades	≥Grade 3	All grades	≥Grade 3
Hypertension	18 (81.8)	8 (36.4)	9 (81.8)	4 (36.4)	9 (81.8)	4 (36.4)
Diarrhea	17 (77.3)	4 (18.2)	10 (90.9)	3 (27.3)	7 (63.6)	1 (9.1)
Hypothyroidism	12 (54.5)	4 (18.2)	7 (63.6)	3 (27.3)	5 (45.4)	1 (9.1)
Proteinuria	10 (45.5)	4 (18.2)	6 (54.5)	3 (27.3)	4 (36.4)	1 (9.1)
Hand–foot syndrome	8 (36.4)	–[A]	5 (45.4)	–[A]	3 (27.3)	–[A]
Hoarseness	6 (27.3)	0	4 (36.4)	0	2 (18.2)	0
Appetite loss	6 (27.3)	0	4 (36.4)	0	2 (18.2)	0
Fatigue	4 (18.2)	0	2 (18.2)	0	2 (18.2)	0
Fever	2 (9.1)	1 (4.5)	1 (9.1)	1 (9.1)	1 (9.1)	0
Vomiting	2 (9.1)	0	1 (9.1)	0	1 (9.1)	0
Sinusitis	1 (9.1)	0	0	0	1 (9.1)	0
Stomatitis	1 (9.1)	0	0	0	1 (9.1)	0
Otitis externa	1 (4.5)	1 (4.5)	1 (9.1)	1 (9.1)	0	0
Cerebral infarct	1 (4.5)	1 (4.5)	1 (9.1)	1 (9.1)	0	0

Data are presented as n (%). [A]There was no classification of ≥Grade 3 for hand–foot syndrome according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. TKI, tyrosine kinase inhibitor.

(77.3%), hypothyroidism (54.5%), proteinuria (45.5%), and hand–foot syndrome (36.4%) were common in both groups, followed by fatigue (18.2%), decreased appetite (27.3%), hoarseness (27.3%), vomiting (9.1%), fever (9.1%), and cerebral infarction (4.5%). The incidence of these adverse events was comparable between the TKI(−) and TKI(+) groups.

Treatment of Axitinib-Induced Hypertension

The number of antihypertensive drugs used to achieve blood pressure control after initiation of axitinib increased significantly in all patients (1.0±1.0 vs. 1.7±1.1; P<0.05; **Figure 4A**). There was a tendency for an increase in the number of antihypertensive drugs used in the TKI(−) group (0.9±0.9 vs. 1.6±0.8; P=0.052; **Figure 4B**) and TKI(+) group (1.1±1.2 vs. 2.0±1.2; P=0.051; **Figure 4C**), but the differences were not statistically significant. **Figure 5** shows the proportion of major classes of antihypertensive drugs administered before and after initiation of axitinib. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and Ca^{2+} channel blockers were commonly administered. In 68% of patients, target SBP <140 mmHg was achieved within 1 month. Conversely, 1 patient with poorly controlled blood pressure developed serious cerebral infarction 28 months after initiation of axitinib.

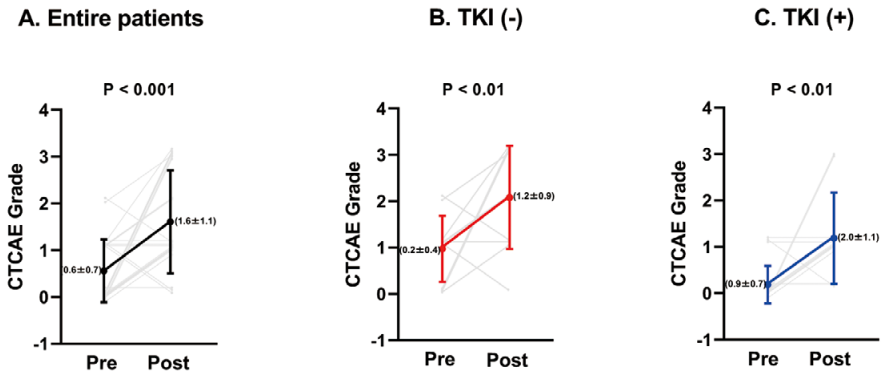

Figure 3. Changes in the grade of hypertension after initiation of axitinib in all patients (**A**) and in patients who did not (**B**) or did (**C**) receive a tyrosine kinase inhibitor (TKI) as part of the first-line treatment regimen. The grade of hypertension was plotted for individual patients, with the mean (±SD) grades calculated and connected by straight lines. CTCAE, Common Terminology Criteria for Adverse Events version 5.0.[20]

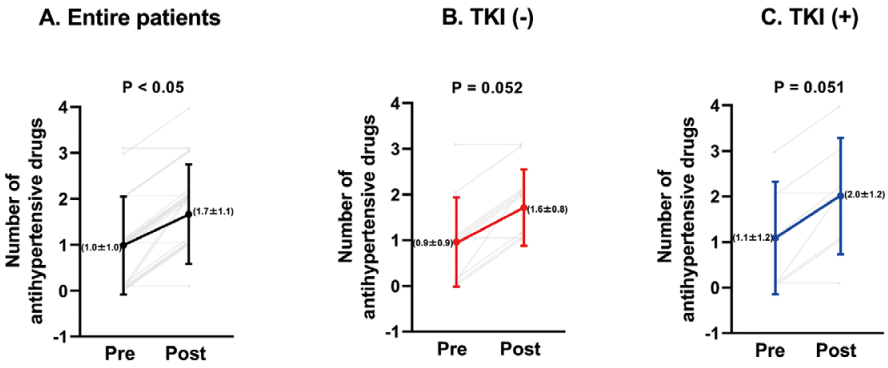

Figure 4. Changes in the number of antihypertensive drugs after initiation of axitinib in all patients (**A**) and in patients who did not (**B**) or did (**C**) receive a tyrosine kinase inhibitor (TKI) as part of the first-line treatment regimen. The number of antihypertensive drugs is plotted for individual patients, with the mean (±SD) number calculated and connected by straight lines.

The mean period of axitinib treatment was 380±284 days, with the shortest duration being 77 days. In addition, the mean period of axitinib treatment tended to be longer in patients who experienced hypertension than that in patients who did not (400.2±284.1 vs. 171.5±60.5 days; P=0.09). Fourteen patients (63.6%) developed PD, and 5 patients (22.7%) discontinued axitinib due to adverse events: diarrhea in 3 patients (13.6%), proteinuria in 1 patient (4.5%), and cerebrovascular disease in 1 patient (4.5%). There was no case in which uncontrolled blood pressure led to an interruption of axitinib treatment in this study. In 11 patients (50%), the dosage of axitinib was reduced because of a combination of 2 or 3 adverse events.

Discussion

In the present study, axitinib elevated blood pressure, regardless of a prior regimen with or without TKIs. Axitinib-induced hypertension developed in 81.8% of patients, and 36.4% of patients experienced Grade 3 hypertension. Accordingly, the grade of hypertension was elevated after initiation of axitinib, and the number of antihypertensive drugs used increased across all patients. Compared with previous studies reporting that the incidence of axitinib-induced hypertension was up to 60%,[10,16–19] the incidence of axitinib-induced hypertension in the present study was much higher. Importantly, our data draw attention to the fact that axitinib significantly worsened hypertension even in patients who had prior TKI used as part of first-line therapy (**Figures 2**,**3**).

VSP inhibition induces arterial hypertension via multiple molecular mechanisms.[5,22] VSP inhibitors reduce the production of vasodilators such as nitric oxide and prostaglandin I_2, and enhance the production of vasoconstrictors such as endothelin-1 and oxidative stress, leading to increased vascular tone and arterial remodeling. Microvascular rarefaction may contribute to sustained elevation of blood pressure. In addition, VSP inhibitors reduce pressure natriuresis and impair lymphatic function, leading to exacerbation of fluid volume overload. All these processes in

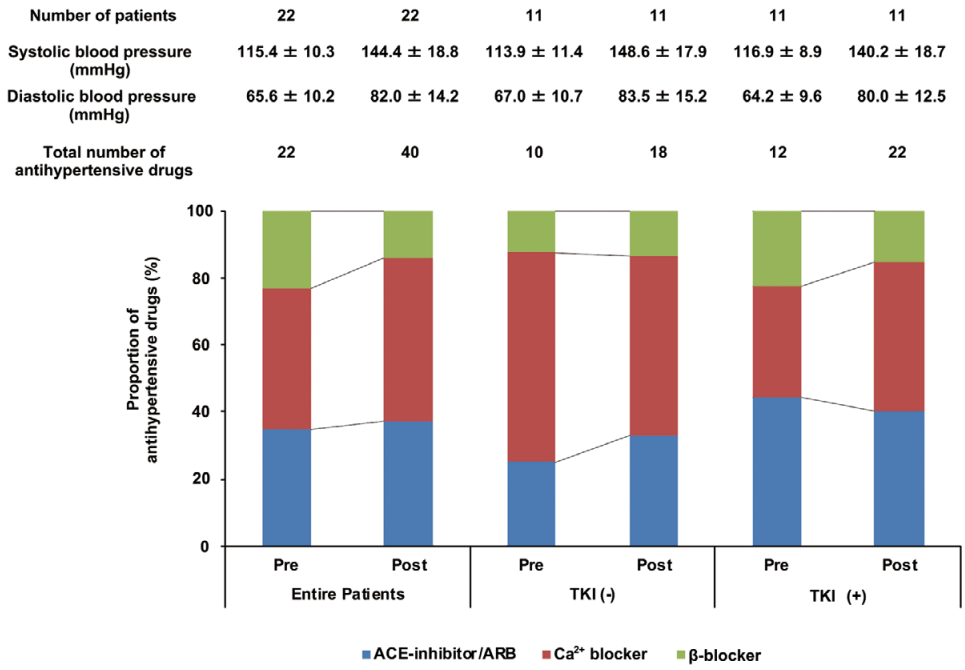

Figure 5. Proportion of the major classes of antihypertensive drugs administered before and after initiation of axitinib in all patients and in patients who did not or did receive a tyrosine kinase inhibitor (TKI) as part of the first-line treatment regimen. Blood pressure data are given as the mean±SD. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

combination could elevate blood pressure.[5,22] Axitinib is a potent and selective inhibitor of VEGFR-1, -2, and -3, and inhibits autophosphorylation of these receptors at picomolar concentrations; the half-maximal inhibitory concentration (IC_{50}) for axitinib is lower than for other TKIs such as sunitinib, sorafenib, and ponatinib.[8,9] Potent inhibition of VEGFRs by axitinib accounts for the higher incidence and grade of hypertension, as shown in the present study.

Given that hypertension reflects the on-target inhibitory effect of axitinib on VEGFRs, elevation of blood pressure after axitinib treatment may be associated with improved drug response and clinical outcome. In a post hoc landmark analysis from the AXIS trial, median OS was significantly longer in patients with DBP >90 mmHg (20.7 months) than in those with DBP <90 mmHg (12.9 months) in the axitinib group (hazard ratio 0.627; 95% confidence interval [CI] 0.507–0.776; P<0.0001), although mPFS was comparable between the DBP subgroups.[11] In the present study, of the 4 patients who did not experience DBP >90 mmHg, 2 patients had PD and 2 patients died during chemotherapy with axitinib. In addition, the mean period of axitinib treatment in patients who experienced hypertension tended to be longer, supporting the idea that blood pressure elevation may be associated with clinical outcome. In contrast, an Italian multi-institutional retrospective analysis enrolling 62 patients with metastatic RCC demonstrated that hypertension was not associated with better outcome in axitinib-treated patients.[19] Clinical trials and real-world experiences of much larger populations of RCC patients will be needed to determine whether blood pressure may be used as a predictive marker to identify patients who could benefit from axitinib treatment.

In clinical practice, the optimal goal for blood pressure lowering remains unclear for the best management of RCC patients who have TKI-induced hypertension. According to meta-analyses of clinical trials involving sunitinib and sorafenib, the incidence of arterial thromboembolic events, such as arterial thrombosis, cerebral ischemia/infarct, and myocardial ischemia/infarct, was 1.4% and the relative risk was 3.03 (95% CI 1.25–7.37; P=0.015).[23] In the present study, 36.4% of patients (n=8) had Grade 3 hypertension, and 1 patient with uncontrolled hypertension developed cerebral infarct. The life expectancy of cancer patients has been extended,[24] and the duration of TKI treatment of RCC patients is becoming longer and longer. Obviously, proper monitoring and management of blood pressure throughout the treatment period is crucial to reduce serious cardiovascular complications and to continue optimal anticancer strategies for longer periods.

The present study has several limitations. First, it was a single-center observational study. Second, we acknowledge that the relatively small number of patients may have affected the results and reduced the statistical power of the study. Individual TKIs for the first-line treatment may have different effects on axitinib-induced hypertension. More extensive clinical experience and prospective studies in much larger patient populations are needed to uncover the true picture of hypertension and hypertension-related sequelae in RCC patients treated with axitinib and other VSP inhibitors.

In conclusion, axitinib increased arterial blood pressure and the number of antihypertensive drugs used, regardless of the prior use of TKIs. Because RCC patients live longer and uncontrolled hypertension can lead to arterial throm-

boembolic events, clinicians need to provide the best monitoring and management of blood pressure to improve cardiovascular health throughout the treatment period.

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Disclosures

H.A. has received lecture fees from Pfizer Japan Inc. H.A., I.K. are members of *Circulation Reports*' Editorial Team. The remaining authors have no conflicts of interest to declare.

IRB Information

This study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (Reference no. 2020222NI).

Author Contributions

H. Kadowaki and J.I. contributed equally to this study. H.A. and I.K. conceived this study. H. Kadowaki, J.I. analyzed the data. H.Y., A.S.-K., M.U., R.M., Q.L., H. Matsunaga, H. Maki helped analysis and interpretation of the data. Y.S., H. Kume advised on this study. H. Kadowaki, J.I., H.A. wrote the draft of this manuscript.

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