Predictive factor and antihypertensive usage of tyrosine kinase inhibitor-induced hypertension in kidney cancer patients

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The predictive factor and antihypertensive usage for tyrosine kinase inhibitor-induced hypertension in kidney cancer patients

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Short title: The predictive factor for TKI-induced hypertension

Abstract

Hypertension is the common adverse event associated with vascular endothelial growth factor receptor-tyrosine kinase inhibitors. The present study was performed to identify the predictive factor(s) of tyrosine kinase inhibitor-induced hypertension and to determine the classes of antihypertensive agents that show the best efficacy against this hypertension. We retrospectively examined charts of 50 cases with vascular endothelial growth factor receptor-tyrosine kinase inhibitor treatment. The relation between backgrounds and tyrosine kinase inhibitor-induced hypertension and effect of antihypertensive agents administered were analyzed. High systolic blood pressure at baseline was a predictive factor for hypertension. There was no difference between calcium channel blockers and angiotensin receptor II blockers as first-line antihypertensive agents for control of the hypertension. Our findings may be helpful for predicting the onset of tyrosine kinase inhibitor-induced hypertension and for management with primary use of either calcium channel blockers or angiotensin II receptor blockers.

Introduction

It had been suggested that antitumor agents do not have a beneficial effect on patient survival in cases of kidney cancer. Only cytokine therapies, such as interferon alpha and interleukin-2, have been used for metastatic or surgically unresectable kidney cancer (MKC) patients. However, these agents show insufficient efficacy [1-3]. Since the phase III trial investigating the effects of sorafenib on MKC, vascular endothelial growth factor (VEGF) signaling pathway inhibitors emerged as leading treatments for MKC [4-8]. Three VEGF receptor-tyrosine kinase inhibitors (VEGFR-TKI), i.e, sorafenib, sunitinib, and axitinib, are available for MKC in Japan as of 2012. The affinity and selectivity of VEGFR-TKI for VEGFR are different, and accordingly the incidence and severity of adverse events (AE) are also different [5-7]. Hypertension (HT) is the most common AE associated with VEGFR-TKI, and it sometimes becomes a critical factor of discontinuation of VEGFR-TKI [5-8]. On the other hand, the onset of HT after initiation of VEGFR-TKI was reported as a possible biomarker of good response to VEGFR-TKI [9]. Therefore, the control of HT is very important for continuation of VEGFR-TKI and to achieve the best outcome in MKC treatment. The present study was performed to identify the predictive factor(s) of

VEGFR-TKI-induced HT, and to determine the classes of antihypertensive agents (AHTA) that show the best efficacy against this secondary HT.

Patients and Methods

Study population

All studies were performed retrospectively in Kanazawa University using charts of patients who were hospitalized at the Department of Urology. MKC patients who underwent VEGFR-TKI (sorafenib, sunitinib, and axitinib) therapy were analyzed. The AHTA administered were categorized according to their mechanisms of action.

Definition of HT

HT was defined as systolic blood pressure (BP) > 140 mmHg corresponding to Grade 2 of the National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0. Our department policy of starting AHTA administration was also the same as the definition of HT. BP of all cases was reviewed before VEGFR-TKI administration (baseline), between the onset of *de novo* HT and starting AHTA administration, and when the HT improved after AHTA administration. The average BP levels at identical times on 3 consecutive days were calculated and used for analyses, but single BP measurements were also used if the patient was discharged and became

an outpatient.

Statistical analysis

Statistical analyses were performed using commercially available software (Prism). Comparisons between two groups were performed by unpaired two-sided *t* test, Fisher's exact test, and chi-square test for trends. The probability of administration of AHTA was estimated using the Kaplan–Meier method. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

Patient characteristics

Fifty VEGFR-TKI administration events from 41 patients could be analyzed. Patient demographic data are shown in **Table 1**.The numbers of cases of sorafenib, sunitinib, and axitinib administration were 18, 27, and 5, respectively. Twenty-two patients had preexisting HT and one or two AHTA had already been prescribed. The possibility of AHTA administration is shown in **Fig. 1a**.

Predictive factor of VEGFR-TKI-induced HT

Of 50 cases, 20 had HT after VEGFR-TKI administration, and their backgrounds were compared with those of 30 non-HT cases (**Table 2**). Median systolic BP at baseline was significantly high in 20 HT cases, and the distributions of systolic BP in the non-HT and HT groups are shown in **Fig. 1b**. Two had Grade 2 HT at baseline and started AHTA after deterioration of HT to Grade 3 (systolic BP > 160 mmHg). The distributions of BP at baseline and before AHTA administration in the HT group are also shown in **Fig. 1c**.

Usage of AHTA

The differences in efficacy among AHTA administered in 13 cases of *de novo* HT, i.e., with no AHTA administration before initiation of VEGFR-TKI, were analyzed. First-line AHTA was either calcium channel blockers (CCB) or angiotensin receptor II blockers (ARB). There was no significant difference between control rate of CCB and ARB as first-line treatment (3 of 8 in CCB and 3 of 5 in ARB, $P = 0.5921$, **Fig. 2**).

Discussion

It is important to identify predictive factors for key AE associated with VEGF-TKI to prevent discontinuation and to predict the population likely to show a good response to these agents. Moreover, it may contribute to better outcome. In axitinib treatment for Japanese MKC patients, Tomita et al. suggested that baseline proteinuria and soluble VEGFR-2 levels may be predictive factors of axitinib-induced proteinuria, which may also be a predictive factor of good response to axitinib [10]. With regard to HT, a study of the VEGFR-TKI cediranib for non-small cell lung cancer indicated that predictors of VEGFR-TKI-induced HT were Eastern Cooperative Oncology Group performance status 0, female, normal LDH, and no prior peripheral vascular disease [11]. A meta-analysis of sunitinib indicated a significantly higher incidence of sunitinib-induced HT in MKC than gastrointestinal stromal tumors [12]. These studies indicated that predictors of VEGFR-TKI-induced HT in MKC patients should exist, and should be identified for extended VEGFR-TKI use in MKC. In the present study, high baseline systolic BP was the only predictive factor for VEGFR-TKI-induced HT. This result is reasonable, and indicated that evaluation of BP at baseline is important for management of VEGFR-TKI administration. As there is still

controversy regarding the optimal treatment for VEGFR-TKI-induced HT, we investigated which category of AHTA is preferable for treatment of secondary HT based on the charts of 13 *de novo* HT cases. As expected, two major categories of AHTA were used as first-line therapy for VEGFR-TKI-induced HT, i.e., CCB and ARB, and there was no difference in efficacy between these two AHTA categories. Although some review articles proposed usage of AHTA for VEGFR-TKI-induced HT, there is no evidence that the specific usage of AHTA should be applied for VEGFR-TKI-induced HT [13-15]. However, the unique situation of VEGFR-TKI-induced HT should be taken into consideration. It has been reported that ARB may have antitumor effects through the inhibition of angiotensin II signaling [16]. A systematic review indicated that ARB could improve progression-free survival in MKC patients, and that ARB administration was protective against prostate specific antigen failure in prostate cancer patients [17]. Moreover, ARB could decrease pressure in the glomerulus, and then reduce proteinuria, consequently inhibiting the deterioration of renal function [18, 19]. As proteinuria is a critical AE of VEGFR-TKI as well as HT [7, 10], ARB may be preferable for patients treated with VEGFR-TKI. On the other hand, ARB cannot be used for patients with bilateral renal artery stenoses or solitary kidney associated with renal artery stenosis, or for patients with elevated creatinine level > 2.0 mg/dL, and CCB may be

appropriate in such cases. Although this was a retrospective study with a small sample size, we showed that baseline BP may predict VEGFR-TKI-induced HT, and that there is no difference in efficacy for VEGFR-TKI-induced HT between CCB and ARB. Our findings may be helpful for clinicians to predict the onset of VEGFR-TKI-induced HT and for management with primary use of either CCB or ARB.

Conflict of Interest

The authors declare that they have no conflict of interest.

Table 1. Patient demographics

n		50
Median age, yr		65 (26 – 85)
Gender	male	43
	female	7
Prior nephrectomy	yes	30
	no	20
TKI	sorafenib	18
	sunitinib	27
	axitinib	5
Median TKI administration days		102 (7 – 1117)
Median initial BP	systolic	116 (96 – 157)
	diastolic	72 (57 – 90)
Number of prior AHTA	0	28
	1	13
	2	9
Prior AHTA	CCB	17
	ARB	9[†]
	ACEI	1
	others	4
TKI-induced HT	yes	20
	no	30

ACEI = angiotensin converting enzyme inhibitors. Values in parentheses indicate range. [†]One mixture of ARB and diuretic was included.

Table 2. Comparison of backgrounds between HT and non-HT patients

		no HT	HT	P
n		30	20	
Median age, yr		65 (26 – 80)	66 (47 – 85)	0.5992
Gender	male	26	17	1
	female	4	3	
Prior nephrectomy	yes	17	13	0.7688
	no	13	7	
TKI	sorafenib	11	7	0.9923
	sunitinib	16	11	
	axitinib	3	2	
Median TKI administration days		69 (5 – 1047)	188 (21 – 1117)	0.1895
Median initial BP	systolic	114 (96 – 133)	122 (104 – 157)	0.0104
	diastolic	70 (58 – 83)	74 (57 – 90)	0.2555
Number of prior AHTA	0	15	13	0.3486
	1	10	3	
	2	5	4	
Administered AHTA	CCB	13	4	0.3127
	ARB	5[†]	4	
	ACEI	0	1	
	Others	2	2	

Values in parentheses indicate range. [†]One mixture of ARB and diuretic was included.

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Figure legends

Fig. 1 The possibility of AHTA administration is shown using the Kaplan–Meier method (a). Average systolic BP at baseline in non-HT ($n = 30$) and HT ($n = 20$) groups are shown (b). Average systolic and diastolic BP at baseline and before AHTA administration in the HT group are shown (c).

Fig. 2 AHTA administered for EGFR-TKI-induced *de novo* HT are shown. Either CCB or ARB was administered for *de novo* HT as first-line therapy, and second- and third-line AHTA were added if necessary.

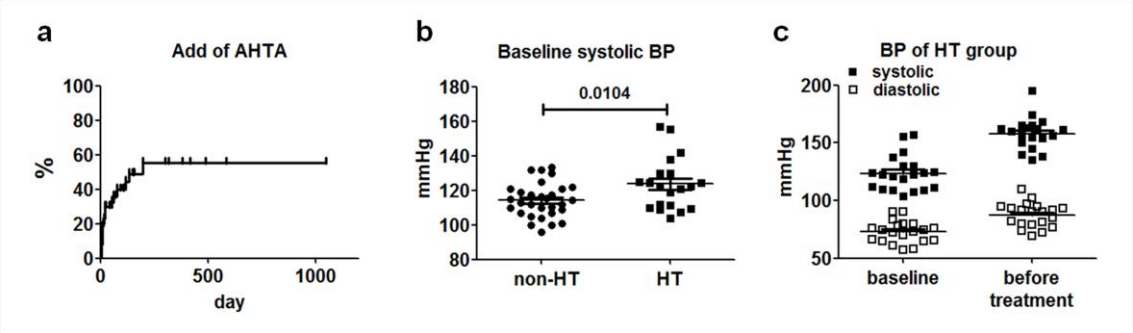
a
Add of AHTA
%
day
b
Baseline systolic BP
0.0104
mmHg
non-HT
HT
c
BP of HT group
systolic
diastolic
mmHg
baseline
before treatment

Fig. 1

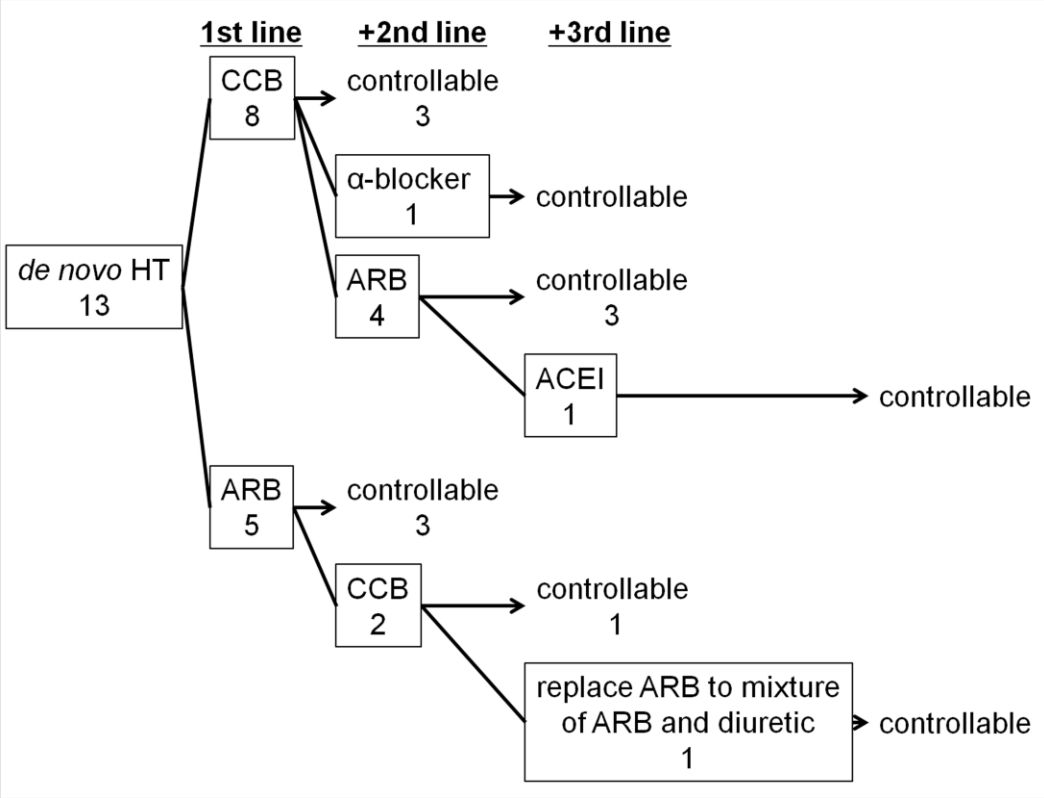
1st line
+2nd line
+3rd line
de novo HT 13
CCB 8
controllable 3
α-blocker 1
controllable
ARB 4
controllable 3
ACEI 1
controllable
ARB 5
controllable 3
CCB 2
controllable 1
replace ARB to mixture of ARB and diuretic 1
controllable

Fig. 2