RESEARCH LETTER

Changes in central and peripheral blood pressure parameters during antiangiogenic treatment of metastatic renal cell carcinoma

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Introduction The current guidelines of the European Society for Medical Oncology recommend antiangiogenetic drugs that inhibit the vascular endothelial growth factor (VEGF) receptor tyrosine kinase as the basis for the treatment of metastatic kidney cancer. Arterial hypertension is the most common adverse effect of treatment with VEGF inhibitors.[1] Several mechanisms that may lead to increased pressure in patients receiving this treatment have been identified, the most important being a reduction in nitric oxide availability[2] and an increase in endothelin concentrations.[3] Almost every patient treated with antiangiogenic drugs has an absolute increase in blood pressure (BP).[4] Research has shown that hypertension is directly associated with the mechanism of action of antiangiogenic drugs. Hence, it has been hypothesized that elevated BP may be a good indicator of the overall blockade of VEGF-dependent pathways as well as of response to treatment of an underlying disease.[5] Several studies have shown that patients with arterial hypertension induced by angiogenesis inhibitors have better treatment outcomes, measured in terms of overall and progression-free survival, than patients without a significant increase in BP.[6]

An increase in office BP during the use of angiogenesis inhibitors has been demonstrated in numerous studies. However, data on changes in central pressure and aortic compliance during the administration of these drugs are lacking. Therefore, the aim of our research was to assess changes in central BP, central pulse pressure, augmentation index, and pulse wave velocity in patients with renal cell carcinoma, after initiation of treatment with angiogenesis inhibitors.

Patients and methods We enrolled 35 patients with metastatic renal cell carcinoma scheduled to receive treatment with tyrosine kinase inhibitors (sunitinib, sorafenib, or pazopanib). All patients were investigated at baseline and 14 days after the commencement of treatment. Volunteers underwent medical history taking, physical examination, basic laboratory and imaging tests necessary to assess eligibility for the study, as well as arterial pressure and pulse wave measurements.

The brachial artery pressure was measured in accordance with the current guidelines of the European Society of Hypertension. Measurements were made using Omron 705 IT (Omron Healthcare, Kyoto, Japan).

Pulse wave analysis was performed using the Sphygmocor CPV system (AtCor Medical, West Ryde, Australia). The pulse wave was recorded in the right radial artery using an applanation tonometer. The measurement was done at least twice, and the result with a higher quality index (at least 90%) was selected. Pulse wave velocity was measured at the section between the carotid and femoral artery using Sphygmocor CPV. It was calculated as the ratio of the distance covered by the pulse wave between the examined arteries and the time in which the pulse wave covered this distance.

All participants were fully informed about the aim of the study and signed a consent form. The study was approved by the local bioethics committee (decision no., 316/14).

Statistical analysis Statistical analysis was performed using the STATISTICA 13.1 software (TIBCO Software, Palo Alto, California, United States). The normality of the distribution of differences between individual parameters was assessed

TABLE 1 Central and peripheral pressure parameters and pulse wave velocity at baseline (V_0) and 2 weeks after treatment initiation (V_1) in patients with and without hypertension

Parameter	Hypertension (n = 28)			No hypertension (n = 7)		
	V_0	$\Delta(V_1–V_0)$	*P* value	V_0	$\Delta(V_1–V_0)$	*P* value
bSBP, mm Hg	128.5 (119.5; 141)	17 (8; 22)	<0.001	125 (115; 138)	8 (0; 22)	0.17
bDBP, mm Hg	78 (70.5; 90)	8.5 (2;18)	<0.001	77 (53; 88)	7 (–6; 23)	0.17
AoSBP, mm Hg	116 (107; 128)	18.5 (10; 25)	<0.001	109 (102; 121)	5 (1; 26)	0.09
AoDBP, mm Hg	79 (70.5; 91.5)	8.5 (1.5; 17.5)	<0.001	79 (54; 89)	5 (–6; 24)	0.31
AIx@75, %	22.5 (17; 33.5)	4 (1.5; 14)	0.039	15 (11; 30)	2 (–3; 7)	0.67
PWV, m/s	10.45 (8.6; 12.6)	1.4 (0.3; 3.1)	<0.001	9.3 (6.7; 11.7)	1.1 (–0.3; 3)	0.47

Data are presented are median (first quartile; third quartile).

Abbreviations: AoDBP, aortic diastolic blood pressure; AIx@75, augmentation index corrected for heart rate; AoSBP, aortic systolic blood pressure; bDBP, brachial diastolic blood pressure; bSBP, brachial systolic blood pressure; PWV, pulse wave velocity

using the Shapiro–Wilk test. Due to nonnormal distribution of some of the parameters, the significance of differences between these parameters was checked with the Wilcoxon test. For all statistical tests, a *P* value of less than 0.05 was considered significant.

Results The results of 35 patients (28 men and 7 women) were included in the final analysis. In this group, 26 participants were taking sunitinib (74%); 7, sorafenib (20%); and 2, pazopanib (6%).

During referral for antiangiogenic treatment, 80% of patients were diagnosed with arterial hypertension, and most of them were treated with 2 or 3 antihypertensive drugs.

Central and peripheral pressure at baseline did not differ between patients with and without hypertension (TABLE 1). The mean office BP in patients with hypertension was 130/78 mm Hg, which indicates good BP control at baseline.

The results of central BP, peripheral BP, and pulse wave velocity measurements in patients with and without hypertension are presented in TABLE 1. During the study, 54% of patients were diagnosed with therapy-induced hypertension, defined as de novo hypertension (BP ≥140/90 mm Hg) or an increase in BP above 140/90 mm Hg in patients with good BP control at baseline.

After 2 weeks of drug administration, the brachial artery pressure increased by a median systolic pressure of 14 mm Hg and diastolic pressure of 8 mm Hg (*P* <0.001). The increase was evident in the hypertension group (ie, 17/8.5 mm Hg) but not in patients without hypertension.

The observed increase in BP was more notable in patients with previously diagnosed hypertension, while it was not significant in patients without hypertension.

The augmentation index corrected for heart rate increased in the hypertension group by a median of 4%, which corresponds to a relative increase of 17.8% (*P* = 0.039), and the pulse wave velocity increased by a median of 1.4 m/s from the baseline value of 10.45 m/s (*P* <0.001). Both parameters did not increase significantly in the group without hypertension, but the number of participants was too low to achieve adequate statistical power.

Discussion Despite numerous studies on arterial hypertension induced by angiogenesis inhibitors, there are little data reporting the exact values of the observed increase. The change in peripheral pressure shown in our study was one of the most significant ones reported in the literature. Szmit et al[7] described an average increase in pressure of 10.2/9.5 mm Hg after 28 days of sunitinib administration in patients with kidney cancer. On the other hand, Veronese et al,[8] who analyzed BP in 20 patients treated with sorafenib due to various solid tumors, reported an increase in BP by 20.6/7.9 mm Hg (*P* <0.001) during the first 3 weeks of therapy.

In our study, the increase in BP led to the diagnosis of therapy-induced hypertension, that is, de novo hypertension or deterioration of hypertension control in previously diagnosed patients. When the criterion of an increase above 140/90 mm Hg for systolic and diastolic BP was applied, therapy-induced hypertension was reported in 19 participants (54%), which is a much higher percentage than that observed in clinical trials on angiogenesis inhibitors. In meta-analyses, hypertension as a complication of therapy was reported in 21.6% to 38.2% of participants.[9,10] This difference is due to the use of various criteria for hypertension in clinical trials. According to the Common Terminology Criteria for Adverse Events, arterial hypertension was defined as an increase in BP above 150/100 mm Hg or an increase in diastolic BP by 20 mm Hg. In most clinical trials, patients with other than mild hypertension and cardiovascular history were excluded. In this study, we excluded only patients with uncontrolled hypertension, while enrolling those who required even intensive antihypertensive therapy. In studies adopting similar hypertension criteria during treatment with angiogenesis inhibitors, a similar rate of treatment-induced hypertension was noted, ranging from 49% to 58% of participants.[7,11] The criteria for

assessing an increase in BP used in our study are valid and commonly used in Europe for the diagnosis and control of hypertension.

The most clinically relevant finding of this study is that patients with previously diagnosed hypertension are at risk of deterioration, even if BP control was good before treatment. This is important because the currently estimated number of individuals with hypertension is 1.39 billion worldwide.[12] We suggest that patients with a history of hypertension should be monitored more closely even if BP control was satisfactory before the start of anticancer treatment.

The observed effect of angiogenesis inhibitors on the parameters of central pressure as well as a strong association between a high increase in the augmentation index and elevation in central systolic BP suggest the leading role of vasoconstriction in inducing hypertension in these patients. It is unclear which mechanism plays a more important role: an increase in endothelin activity or a decrease in the availability of nitric oxide. However, they both lead to similar hemodynamic effects, identical to those observed in our study.

There are currently no clear guidelines as to which antihypertensive drugs to choose for use in hypertension caused by angiogenesis inhibitors. It is believed that in the absence of evidence favoring one particular drug over another, general guidelines on hypertension should be followed. Any suggestions available in the literature are derived from theoretical premises. It seems that due to the inhibition of nitric oxide secretion by angiogenesis inhibitors, the best drugs would be those that increase its bioavailability. One example among the first-line drugs for hypertension is nebivolol, which has an exact opposite effect on central pressure and its parameters to that caused by angiogenesis inhibitors.

The limitation of the study is a small sample size, which was due to the limited availability of volunteers with renal cancer scheduled for treatment with antiangiogenic drugs. Nevertheless, the obtained results provide an excellent basis for further research, which may elucidate the exact pathomechanism of the observed changes in central and peripheral BP parameters.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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