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Authors: Dawid Lipski, Paweł Uruski, Piotr Tomczak, Justyna Adamiak, Rodryg Ramlau, Andrzej Tykarski

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

Dawid Lipski\textsuperscript{1}, Paweł Uruski\textsuperscript{1}, Piotr Tomczak\textsuperscript{2}, Justyna Adamiak\textsuperscript{3}, Rodryg Ramlau\textsuperscript{2}, Andrzej Tykarski\textsuperscript{1}

Affiliations

1. Department of Hypertensiology, Angiology and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland
2. Department of Oncology, Poznan University of Medical Sciences, Poznan, Poland
3. Department of Physical Medicine and Biological Recovery, University of Physical Education, Cracow, Poland

Corresponding author

Dawid Lipski M.D., M.Sc., Ph.D., Department of Hypertensiology, Angiology and Internal Medicine, Poznan University of Medical Sciences, ul. Długa ½, 61-848 Poznań, tel. +48 61 854 90 90, e-mail: dlipski@ump.edu.pl

Conflict of interest: none declared.

Short title: Blood pressure on antiangiogenic treatment of renal cell carcinoma
**Introduction**

In current European Society for Medical Oncology guidelines from 2016 angiogenesis inhibitors, in the form of inhibitors of tyrosine kinase associated with vascular-endothelial growth factor (VEGF) receptors, are the basis for the treatment of metastatic kidney cancer. Arterial hypertension is the most commonly observed adverse effect of treatment with VEGF inhibitors [1]. Several mechanisms have been identified that may lead to increased pressure during such treatment. The most important is a decrease in the nitric oxide availability [2] and an increase in endothelin concentration [3]. Almost every patient has an absolute increase in blood pressure (BP) [4]. Research shows that hypertension results directly from the mechanism of action of anti-angiogenic drugs. Hence, it has been hypothesized that the increase in BP may be a good indicator of the overall blockade of VEGF-dependent pathways and of the response to the treatment of the underlying disease [5]. Several studies have shown that patients with arterial hypertension induced by angiogenesis inhibitors had better treatment outcomes, measured in terms of overall survival and progression-free survival, than patients, whose BP did not increase significantly [6].

An increase in office BP during the use of angiogenesis inhibitors has been demonstrated in many studies. There is a lack of studies on changes in central pressure and aortic compliance during the administration of these drugs. The aim of the study 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**

Thirty five patients with metastatic renal cell carcinoma that were qualified to the treatment with tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib) were enrolled in the study. All participants were fully informed about aims of the study and signed a consent form. The study project received a positive opinion from the Local Bioethics Committee (decision 316/14). All patients were investigated before treatment - visit 0 (V_0) and 14 days after the start of drug intake - visit 1 (V_1).

Volunteers underwent medical history and physical examination, basic laboratory and imaging tests necessary to qualify for the study, as well as the assessment of arterial pressure and pulse wave.

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

Pulse wave analysis was performed using the Sphygmocor CPV system (AtCor Medical, Australia). The pulse wave was recorded on the right radial artery using an applanation tonometer. The measurement was made at least twice and the result with a higher Quality Index (at least 90%) was selected.

The pulse wave velocity was measured on the section between the carotid artery and the femoral artery using the Sphygmocor CPV. The value of this parameter 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.
**Statistical analysis**

Statistical analysis was performed using the STATISTICA 13.1 software (StatSoft). Normality of the distribution of changes of individual examined parameters was checked using the Shapiro-Wilk test. The distribution of some of the parameters and differences were not normal, so the statistical significance of differences between parameters was checked with the Wilcoxon test. For all statistical tests, the values of $p<0.05$ were considered significant.
Results

Final results of 35 patients (28 men and 7 women) were analyzed. In this group 26 participants were taking sunitinib (74%), 7 – sorafenib (20%) and 2 – pazopanib (6%).

At qualification for anti-angiogenic treatment, 80% of patients were diagnosed with arterial hypertension, where most of them were treated with either two or three antihypertensive substances.

The baseline values of central and peripheral pressure in subgroups of patients with concomitant hypertension (HT group) and without hypertension (non-HT) did not differ significantly (table 1). The mean pressure in office measurements in the hypertensive group was 130/78 mmHg which indicates good initial BP control in this group.

The measurements of central BP, peripheral BP and pulse wave velocity in both HT and non-HT groups are also presented in table 1. In the analyzed period 54% of subjects were diagnosed with therapy induced arterial hypertension, defined as de novo hypertension (BP ≥140/90) or BP increase above 140/90 mmHg, with good pre-treatment control.

The observed increase in blood pressure was more expressed in people with previously diagnosed HT and not significant in non-HT group.
Discussion

After 2 weeks of drug administration ($V_1$), the pressure measured on the brachial artery increased significantly, by a median of 14/8 mmHg ($p < 0.001$). The increase was very clear in HT group, i.e. 17/8.5 mmHg and not significant in non-HT group. Despite numerous studies on arterial hypertension induced by angiogenesis inhibitors, there is little data available on the values of the observed increases. The change in peripheral pressure obtained in the study was among the highest of those described in the literature. S. Szmit et al. observed an average increase in pressure after 28 days of sunitinib administration in patients with kidney cancer of 10.2/9.5 mmHg [7]. On the other hand, in a study by M. Veronese et al., where BP was analyzed in 20 patients treated with sorafenib due to various solid tumors, during the first 3 weeks of therapy there was a rise in BP by 20.6/7.9 mmHg ($p < 0.001$) [8].

The increase in BP led to the diagnosis of HT induced by therapy, that is de novo hypertension or deterioration of control in previously diagnosed patients. With the criterion of exceeding 140/90 mmHg for systolic and diastolic pressure respectively, therapy induced HT occurred in 19 participants (54%), which is a much higher percentage than observed in clinical trials of this group of drugs. In meta-analyzes, hypertension as a complication of therapy occurred in 21.6%-38.2% of participants [9,10]. This difference is due to the use of different criteria for hypertension in clinical trials. According to the criteria for adverse drug reactions as defined in the Common Terminology Criteria for Adverse Events, arterial hypertension was diagnosed as an increase in BP above 150/100 mmHg or an increase in diastolic pressure by 20 mmHg. In most clinical trials, patients with other than mild hypertension and cardiovascular history were excluded. In this study, only patients with uncontrolled hypertension were excluded, leaving those who required even very intensive antihypertensive pharmacotherapy. In studies in which similar hypertension criteria were adopted during treatment with angiogenesis inhibitors, a similar percentage of treatment-
induced hypertension of 49% to 58% of participants was observed [7,11]. The criteria for assessing the increase in BP, used by the authors, are valid and commonly used criteria in Europe for the diagnosis and control of hypertension.

The augmentation index corrected for heart rate (AIx@75) increased in HT group by median 4%, which means a relative increase of 17.8% (p=0.039), and the pulse wave velocity from the initial 10.45 increased in median 1.4 m/s (p<0.001). Both parameters did not increase significantly in non-HT group, but the number of participants was too low to reach appropriate power of the test.

The biggest clinical conclusion of this study, is that patients with previously diagnosed hypertension are at risk of deterioration, even if the BP control was good before treatment. This is an important issue, as the estimated number of individuals with hypertension is now 1.39 billion worldwide [12]. We assume that patients with hypertension history should be monitored more closely even if the BP controlled before start of oncologic treatment.

The observed effect of angiogenesis inhibitors on the parameters of central pressure, a high increase in the augmentation index strongly influencing the increase in central systolic BP are the premise for the leading role of vasoconstriction in inducing HT in these patients. It is not clear whether the most important role is played by an increase in endothelin activity or a decrease in the availability of nitric oxide. Both of these lead to similar haemodynamic effects, identical to those obtained in the study.

Until now, no unambiguous guidelines have been established for the choice of antihypertensive drugs for use in hypertension caused by angiogenesis inhibitors. It is believed that in the absence of evidence of better efficacy of particular drugs, general guidelines on hypertension should be followed. The suggestions indicated in the literature result mainly 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 the
bioavailability of this vasodilator. Among the drugs of the first choice in the treatment of hypertension, such a substance is nebivolol, the effect of which on central pressure and its parameters is exactly opposite to that caused by inhibitors of angiogenesis.

The limitation of the conducted study is a modest number of volunteers; the group size was affected by the limited availability of volunteers with renal cancer qualified for treatment with anti-angiogenic drugs. Nevertheless, the obtained results provide an excellent basis for further research, which may allow to learn the exact pathomechanism of the observed changes.
References


Table 1

Central and peripheral pressure parameters and pulse wave velocity at baseline ($V_0$) and 2 weeks after treatment initiation ($V_1$) in the subgroup with coexisting arterial hypertension (n = 28) and without hypertension (n = 7). Values presented are median (first, third quartile).

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>HT</th>
<th>NON-HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>bSBP, mmHg</td>
<td>128.5 (119.5, 141)</td>
<td>125 (115, 138)</td>
</tr>
<tr>
<td>bDBP, mmHg</td>
<td>78 (70.5, 90)</td>
<td>77 (53, 88)</td>
</tr>
<tr>
<td>AoSBP, mmHg</td>
<td>116 (107, 128)</td>
<td>109 (102, 121)</td>
</tr>
<tr>
<td>AoDBP, mmHg</td>
<td>79 (70.5, 91.5)</td>
<td>79 (54, 89)</td>
</tr>
<tr>
<td>Alx@75, %</td>
<td>22.5 (17, 33.5)</td>
<td>15 (11, 30)</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>10.45 (8.6, 12.6)</td>
<td>9.3 (6.7, 11.7)</td>
</tr>
</tbody>
</table>

bSBP – brachial systolic blood pressure, bDBP - brachial diastolic blood pressure, bPP – brachial pulse pressure, AoSBP - aortic systolic blood pressure, AoDBP - aortic diastolic blood pressure, AoPP – aortic pulse pressure, Alx@75 – augmentation index corrected for heart rate, PWV – pulse wave velocity