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Lenvatinib, an oral multi-kinases inhibitor, -associated hypertension: Potential role of vascular endothelial dysfunction

Daisuke Sueta [a], Koichi Suyama [b], Aiko Sueta [c], Noriaki Tabata [a], Takayoshi Yamashita [a], Mai Tomiguchi [c], Takashi Takeshita [c], Mutsuko Yamamoto-Ibusuki [c], Eiichiro Yamamoto [a], Yasuhiro Izumiya [a], Koichi Kaikita [a], Yutaka Yamamoto [c], Seiji Hokimoto [a, *], Hirotaka Iwase [c], Kenichi Tsujita [a]

[a] Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
[b] Kumamoto University Hospital Cancer Center, Kumamoto University, Kumamoto, Japan
[c] Department of Breast and Endocrine Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

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ABSTRACT

Background and aims: Lenvatinib (Lenvima®), an oral multi-kinase inhibitor, is effective in the treatment of differentiated thyroid carcinomas (DTCs). A severe adverse effect of lenvatinib is hypertension, thus limiting its use as an anti-cancer treatment. Although the pathogenesis of hypertension is generally assumed to involve microvascular bed reduction and an increase in peripheral vascular resistance due to a decrease in nitrogen oxide (NOx) production after vascular endothelial growth factor (VEGF) inhibition, the effects of hypertension on vascular endothelial function in actual patients remain unclear. Here, we examined how lenvatinib affects vascular endothelial function.

Methods: Ten consecutive DTC patients who did not take any cardiovascular agents were orally administered 24 mg of lenvatinib once daily. Using an EndoPAT2000® system, we used reactive hyperemia-peripheral arterial tonometry (RH-PAT) and evaluated vascular endothelial function on the basis of the RH-PAT index (RHI). We expressed the results as %RHI, which indicates the change compared with pretreatment levels. Additionally, we measured serum NOx and plasma VEGF concentrations pre- and post-treatment.

Results: All of the patients treated with lenvatinib exhibited significant hypertension; the %RHI levels were significantly decreased the day after treatment with lenvatinib. Furthermore, serum NOx and plasma VEGF concentrations were significantly decreased and increased, respectively, compared with pretreatment levels. These results indicate that hypertension induced by lenvatinib may be caused by a decrease in nitric oxide production, as a result of VEGF inhibition and impaired vascular endothelial function.

Conclusions: We provide the first demonstration that lenvatinib causes hypertension via vascular endothelial dysfunction in human subjects.

1. Introduction

Molecular targeted therapies such as anti-cancer agents and anti-rheumatic drugs, whose use is increasing, induce hypertension with a high frequency. In actual clinical situations, it is important to monitor blood pressure in patients who are administered these drugs. These molecular targeted therapies have been listed as causing secondary hypertension in recent guidelines [1,2]. Bevacizumab (Avastin™) [3] is effective against breast cancer, colon cancer, non-small cell lung carcinoma, ovarian cancer and malignant glioma. Although the primary effect of this drug is on malignant diseases, it is expected to be effective in treating age-related macular degeneration and diabetic retinopathy. This agent, a monoclonal antibody for the vascular endothelial growth factor (VEGF), suppresses angiogenesis and the proliferation/transition of

* Corresponding author. Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan.
E-mail address: shokimot@kumamoto-u.ac.jp (S. Hokimoto).

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cancer by inhibiting VEGF. Its adverse effects include bleeding, such as that from gastrointestinal hemorrhage and hemoptysis, stroke, transient ischemic attack and myocardial infarction. In addition, bevacizumab exerts various clinical effects by reducing vascular function [4], the most well-known of which is hypertension [5,6]. In a meta-analysis including 12,656 cancer patients with bevacizumab, 23.6% of the patients had hypertension, and 7.9% had moderate to severe hypertension [7]. Furthermore, a review by Izzedine et al. has described the incidence of hypertension induced by these anti-VEGF drugs, including multi-drug use [8]. In addition to bevacizumab, sunitinib (Sutent™) [9] is effective against gastrointestinal stromal tumor and renal cell carcinoma, sorafenib (Nexavar™) [10] is effective against renal cell carcinoma and hepatic cell carcinoma. Both of these drugs cause hypertension with a high frequency. The mechanism of antiangiogenic therapy-related hypertension is not fully understood. However, it is thought to be related to VEGF inhibition, which decreases nitric oxide (NO) production in the walls of the arterioles and other resistance vessels [6]. Moreover, this hypertension is assumed to involve impairment in kidney function via micro-thrombosis formation [8]. A recent literature review [2] has reported that bevacizumab causes hypertension in 23.6% of patients, whereas small-molecule tyrosine kinase inhibitors cause hypertension in 15.3% of patients in the case of sorafenib and 21.6% of patients in the case of sunitinib [9].

Lenvatinib (Lenvima™) [11,12] is a novel oral, multi-targeted tyrosine kinase inhibitor that exerts anti-malignant effects by inhibiting many tyrosine kinase receptors, such as VEGF receptors 1, 2, and 3, fibroblast growth factor receptors 1 through 4, platelet-derived growth factor receptor α, rearranged during transfection (RET), and stem cell factor receptor (KIT) signaling networks [13]. In the Phase 3 Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) trial, lenvatinib, as compared with placebo, was associated with significant improvements in progression-free survival ($p < 0.0001$, log-rank test) [11]. Although lenvatinib's usefulness has been demonstrated, adverse effects such as hypertension, proteinuria, hand-foot-mouth syndrome, diarrhea, fatigue/malaise and appetite loss often necessitate the discontinuation of administration. Although the rate of hypertension was high (67.8%) in the SELECT trial [11], subanalysis in the SELECT trial in Japanese patients has indicated hypertension in 86.7% of patients [12]. Although studies on relationship between vascular endothelial dysfunction and bevacizumab [14], sorafenib [15] and sunitinib [16] have been conducted, the clinical use of lenvatinib in Japanese patients is highly suitable for research on VEGF receptor-induced hypertension.

In recent years, reactive hyperemia-peripheral arterial tonometry (RH-PAT) has emerged as a non-invasive measurement of vascular endothelial function that is highly reproducible and easily measured. Bonetti et al. have reported that the RH-PAT index (RHI) is a useful predictor of coronary vascular endothelial dysfunction [17]. Moreover, we have reported that the RHI is significantly correlated with the coronary blood flow reserve in reactive hyperemia induced by adenosine [18]. A study, in which Nω-nitro-L-arginine methyl ester (L-NAME) was administered to healthy subjects and vascular endothelial function was measured by RH-PAT, has indicated that it is an NO-dependent reaction derived from vascular endothelium [19]. In the present study, we sought to examine how lenvatinib affects vascular endothelial function in Japanese subjects by using RH-PAT.

2. Materials and methods

2.1. Study design

This study was a prospective single-center (Kumamoto University Hospital, Kumamoto, Japan), open-label, observational trial to determine the efficacies of lenvatinib on blood pressure and vascular endothelial function. All of the procedures were conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the institutional review board of Kumamoto University, and written informed consent was obtained from each patient or from the family of the patient.

We enrolled 13 consecutive differentiated thyroid carcinoma (DTC) patients at Kumamoto University Hospital between January 2016 and September 2016. We excluded 3 patients because of hypotensive agents' use. The remaining 10 DTC patients (male: $n = 4$ and female: $n = 6$, average age: 75.0 ± 8.8 years), who had undergone molecular targeted therapy using lenvatinib without taking any hypotensive agents, and who did not have a history of cardiovascular diseases, were enrolled. The molecular targeted therapies were conducted at the Department of Breast and Endocrine Surgery and Cancer Center of Kumamoto University Hospital. Vascular endothelial function was measured before and after the initiation of the molecular targeted therapy. The measurements were performed by skilled examiners on subjects in a fasting state in the early morning, as described in detail below.

2.2. Lenvatinib administration

All of the enrolled patients were given lenvatinib (Trade name; Lenvima Capsule™; Eisai Co., Ltd., Tokyo, Japan) at a dose of 24 mg/day. The medications were administered to the patients once daily 30 min after breakfast (approximately 9:00 h).

2.3. Measurement of vascular endothelial functions

We used a RH-PAT to measure vascular endothelial function in human subjects as described in detail previously. The validity of our method is well established [18]. The principle of RH-PAT has been described previously [20].

Briefly, RH-PAT noninvasively measures blood volume changes that accompany pulse waves in the distal finger. The data are automatically analyzed by computer software, in an operator-independent manner (Endo-PAT2000; Itamar Medical, Caesarea, Israel, software versions 3.0.4 and 3.4.4). The RHI was measured using the following method. A blood pressure cuff was placed on the upper arm with the contralateral arm serving as a control. A PAT probe was placed on a finger of each hand. After a 5-min equilibration period, the cuff was inflated to 60 mmHg above the systolic pressure or to 200 mmHg for 5 min and then was deflated to induce reactive hyperemia. The RHI reflected the extent of reactive hyperemia and was calculated as the ratio of the average amplitude of the PAT signal over 1 min, starting 1.5 min after cuff deflation (control arm, A; occluded arm, C) divided by the average amplitude of the PAT signal of a 2.5-min time period before cuff inflation (control arm, B; occluded arm, D). Thus, RHI=(C/D)/(A/B)× baseline correction [18].

2.4. Measurement of blood variables

Blood biochemistry measurements were performed at SRL Inc. (Tokyo, Japan).

2.5. Statistical analysis

The effect of the systolic blood pressure, %RHI and biomarkers were compared by using paired t-tests. The cutoff for statistical significance was $p < 0.05$. All statistical analyses were performed using SPSS software version 23 (IBM Corp., Armonk, NY).