Early Detection of Hypertension in a Patient Treated with Sunitinib by Measuring Cardio-Ankle Vascular Index

Hisashi Masugata,1 Shoichi Senda,1 Takashi Himoto,1 Hiroyuki Okuyama,1 Michio Inukai,1 Koji Murao,2 Naohisa Hosomi,3 Kazushi Yukiiri,3 Masakazu Kohno,3 Ayumu Yamagami,1 Takeaki Kohno1 and Fuminori Goda1

1Department of Integrated Medicine, Kagawa University, Kagawa, Japan
2Division of Endocrinology and Metabolism, Department of Internal Medicine, Kagawa University, Kagawa, Japan
3Department of Cardiorenal and Cerebrovascular Medicine, Kagawa University, Kagawa, Japan

Cardio-ankle vascular index (CAVI) has been established as a marker of arterial stiffness, which is increased in hypertensive patients (Okura et al. 2007). CAVI reflects the stiffness of the aorta, femoral artery, and tibial artery. Sunitinib, multi-targeted tyrosine kinase inhibitor with both anti-angiogenic and anti-tumor activities, has been proved effective in patients with gastrointestinal stromal tumors. However, the treatment with sunitinib is often complicated by side effects such as hypertension. We describe an 84-year-old woman with gastrointestinal stromal tumor, who showed changes in arterial stiffness preceding the appearance of hypertension in the early phase after sunitinib initiation. The patient received sunitinib (50 mg given daily) for gastrointestinal stromal tumor. We assessed the influence of sunitinib on arterial stiffness every 7 days by measuring CAVI. The CAVI, which reflects arterial stiffness, was increased from 9.95 at baseline to 11.65 at 7 days after the initiation of sunitinib, whereas the blood pressure remained unchanged (117/72 and 119/76 mmHg). At 14 days after sunitinib initiation, the blood pressure was increased to 159/89 mmHg, indicating the occurrence of hypertension, while the CAVI was 11.90, the similar level detected at 7 days. Subsequently, sunitinib treatment was discontinued, because of the marked decrease in blood platelets. Both blood pressure and CAVI, together with blood platelets, were restored to the baseline values at 12 days after cessation of sunitinib. In conclusion, the increase in the CAVI preceded the appearance of sunitinib-induced hypertension. Arterial stiffness assessed by CAVI may be useful for early detection of sunitinib-induced hypertension. ——— sunitinib; arterial stiffness; cardio-ankle vascular index; cardiac function; echocardiography.

Received March 18, 2009; revision accepted for publication April 16, 2009.
Correspondence: Hisashi Masugata, M.D., Department of Integrated Medicine, Kagawa University, 1750-1, Miki-cho, Kita-gun, Kagawa 761-0793, Japan.
e-mail: masugata@med.kagawa-u.ac.jp
In the present study, we describe a patient with gastrointestinal stromal tumor, who showed changes in arterial stiffness assessed by CAVI and cardiac dysfunction assessed by echocardiography after sunitinib initiation. Importantly, the increase in arterial stiffness precedes the increase in blood pressure during the early phase of sunitinib treatment.

**Clinical Findings**

An 84-year-old woman had a history of gastrointestinal stromal tumor diagnosed 4 years previously and had been treated with imatinib; however, she was diagnosed as imatinib-refractory, so we began treatment with sunitinib. She had no history of hypertension or heart disease. She had no cardiac symptoms or signs. She was normotensive and showed normal blood examination data and echocardiographic findings before sunitinib initiation. We assessed the influence of sunitinib on her blood pressure and arterial stiffness every 7 days by measuring CAVI while simultaneously monitoring cardiac function using echocardiography. This protocol was approved by the Ethics Committee of Kagawa University. Informed consent was obtained from the patient.

CAVI was recorded using a VaseraVS-1000 vascular screening system (Fukuda Densi, Tokyo, Japan) with the patient resting in a supine position. The principal underlying CAVI has been described previously (Yambe et al. 2004, 2005; Shirai et al. 2006). ECG electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the sternum, and cuffs were wrapped around both arms and both ankles. After automatic measurements were taken, the obtained data were analyzed using VSS-10 software (Fukuda Densi), and the values of right and left CAVIs were calculated. The averages of the right and left CAVIs were used for analyzing the influence of sunitinib on arterial stiffness. Because the values of right and left blood pressure measured at each arm were collected for CAVI determination, we used the averages of the right and left blood pressure to analyze sunitinib-induced changes in the patient’s blood pressure.

Two-dimensional and M-mode echocardiography were performed using the Vivid Seven System (GE; Horten, Norway). We first measured the following left ventricular (LV) structural parameters by M-mode echocardiography: ventricular septal thickness at the chordae tendineae level; LV end-diastolic dimension and LV end-systolic dimension at the chordae tendineae level; LV posterior wall thickness at the chordae tendineae level; the end-systolic dimension of the left atrium; and the dimension of the ascending aorta. The LV ejection fraction (LVEF) was estimated by Teichholz’s method (Teichholz et al. 1976) and was used as the parameter of LV systolic function.

We next measured the parameters of LV diastolic function by recording mitral annular velocities from the apical window using tissue Doppler echocardiography. Sample volumes were located at the septal site of the mitral annulus. The peak early diastolic mitral annular velocity (E’) is widely used as a parameter of LV diastolic function, and a decrease in E’ indicates LV diastolic dysfunction (Sohn et al. 1997; Ommen et al. 2000; Nikitin and Witte 2004).

After the patient started the treatment with sunitinib, she showed a gradual decrease in blood platelets. When the platelets had decreased to 48,000/µL at 16 days after sunitinib initiation (the platelets at baseline: 227,000/µL), we decided to interrupt the sunitinib treatment. The platelet count increased gradually after the interruption of treatment and was restored to 106,000/µL at 28 days after sunitinib initiation (12 days after interruption). We measured the CAVI and echocardiographic parameters at baseline and every 7 days during this period that included the sunitinib treatment and the interruption of treatment. The data are summarized in Figs. 1, 2, and 3.

Although the patient’s blood pressure had hardly

![Fig. 1. Alterations of CAVI and blood pressure during the sunitinib treatment and the interruption of treatment.](image-url)
Changes in Arterial Stiffness during Sunitinib Administration

Fig. 2. Alterations of the left ventricular ejection fraction (LVEF) during the sunitinib treatment and the interruption of treatment.
LVEF decreased quickly in response to the increase in the CAVI at 7 days after sunitinib initiation, and it recovered quickly to the baseline value at 5 days after sunitinib interruption. CAVI: cardio-ankle vascular index.

Fig. 3. Alterations of the peak early diastolic mitral annular velocity (E') during the sunitinib treatment and the interruption of treatment.
E' decreased quickly in response to the increase in the CAVI at 7 days after sunitinib initiation, and it increased quickly to more than the baseline value at 5 days after sunitinib interruption. CAVI: cardio-ankle vascular index.
changed at 7 days after sunitinib initiation, the CAVI increased from 9.95 to 11.65 (Fig. 1). When the CAVI value increased to 11.90 at 14 days after the sunitinib initiation, the blood pressure increased to 159/89 mmHg, indicating the occurrence of hypertension for the first time. After sunitinib treatment was stopped for 17 days, both blood pressure and CAVI decreased quickly and were restored to the baseline values at 28 days after sunitinib initiation (12 days after interruption).

The changes in the echocardiographic parameters, which reflect left systolic function (LVEF) and diastolic function (E‘) over the course of the patient’s sunitinib treatment, are summarized in Figs. 2 and 3, respectively. LVEF, reflecting LV systolic function, decreased quickly from 66% to 60% in response to the increase in the CAVI at 7 days after sunitinib initiation, and decreased further to 58% at 14 days after sunitinib initiation. However, the LVEF increased quickly to the baseline value at 5 days after sunitinib interruption (Fig. 2). Likewise, the changes in E‘ indicated the deterioration and restoration of LV diastolic function, in response to sunitinib administration and its interruption, respectively (Fig. 3). The reversible cardiac dysfunction produced by sunitinib was observed in both systolic and diastolic functional parameters. Thus, cardiac functional parameters changed quickly in accord with the alterations of arterial stiffness assessed by the CAVI. However, the patient had no adverse cardiac symptoms or signs during the administration and interruption of sunitinib.

**Discussion**

In the present study, we have demonstrated the alterations in arterial stiffness in response to sunitinib administration in a patient with gastrointestinal stromal tumor. The new information in this report is that the increase in arterial stiffness in response to sunitinib treatment may precede the appearance of hypertension. Although both pulse wave velocity and CAVI are used to assess arterial stiffening due to arteriosclerosis, the authors of several studies (Yambe et al. 2004; Masugata et al. 2009) reported that the CAVI is less influenced by blood pressure compared to pulse wave velocity. Thus, it may be reasonable that sunitinib-induced alterations of arterial stiffness assessed by the CAVI differ from alterations in blood pressure. The instrument for measuring CAVI can provide both values of CAVI and blood pressure simultaneously. Therefore, CAVI may be promising for early detection of sunitinib-induced hypertension and decision of introduction of antihypertensive agents. An important part of the mechanism of sunitinib-induced hypertension associated with vascular endothelial growth factor inhibition is thought to involve the decreased production of nitric oxide in the wall of arterioles and other resistance vessels (Izzedine et al. 2009). Vascular endothelial growth factor inhibition diminishes nitric oxide (Horowitz et al. 1997). Indeed, the inhibition of vascular endothelial growth factor may cause increased systemic vascular resistance (Gordon and Cunningham 2005) and vascular rarefac-

The increased arterial stiffness may cause increased systemic vascular resistance. The increased arterial stiffness may precede the appearance of sunitinib-induced hypertension.

The relationship between sunitinib and blood pressure has now been established (Izzedine et al. 2009), and clinicians must recognize the growing consensus that sunitinib used to treat cancer may exacerbate cardiac risk factors. Proactive introduction or even prophylactic use of antihypertensive drugs can allow the maintenance of therapy despite the onset of hypertension. However, there are no established data regarding the effective examinations to detect sunitinib-induced hypertension in the early phase of sunitinib administration. Because the CAVI can provide an indication of both arterial stiffness and blood pressure simultaneously, it may be clinically useful to detect sunitinib-induced hypertension in the early phase of sunitinib treatment.

In this report, alterations of cardiac function as well as arterial stiffness appeared quickly after the initiation of sunitinib treatment. Because the patient showed no adverse cardiac symptoms or signs during the sunitinib treatment, the alterations of cardiac function were likely to be slight. However, the slight changes in cardiac function may reflect a sunitinib-induced increase in arterial stiffness and be useful for detecting hypertension in the early phase of sunitinib treatment. An important part of the mechanism of the temporarily impaired cardiac function in this patient probably involved the increased afterload on the left ventricle due to sunitinib-induced arterial stiffening.

Two previous studies (Miyazawa et al. 1980; Ludbrook et al. 1982) have demonstrated that the responses to increased afterload produced by isometric exercise differ between normal subjects and patients with heart disease. In these studies, the LVEF increased in normal subjects but decreased in patients with heart disease in response to increased afterload. Because the patient in the present case report is fairly elderly (84 years old), her baseline cardiac function may have already been impaired. Borlaug et al. (2007) demonstrated that E‘ varied inversely with systemic vascular resistance and vascular stiffness measured by pulse wave velocity. Thus, the decreased E‘ velocity during sunitinib administration in our patient may have been a response to the sunitinib-induced increase in afterload.

Chu et al. (2007) suggested the direct cardiotoxicity of sunitinib by causing mitochondrial injury and cardiomyocyte apoptosis in a mouse model. However, they suggest that hypertension may play a role in myocardial injury and apoptosis and that the contribution of hypertension to sunitinib-associated LV dysfunction needs to be examined further. In our patient, the slight deterioration of cardiac systolic and diastolic function during sunitinib administration was quickly reversed after the interruption of sunitinib treatment. Therefore, hypertension rather than direct cardiotoxicity may have contributed to the alterations of cardiac function. However, it is difficult to diagnose that the patient had no direct cardiotoxicity of sunitinib, because we had no
data other than echocardiographic parameters. It is possible that both sunitinib-induced hypertension and myocardial injury occurred simultaneously. Further studies are needed to examine the timing of the appearance of sunitinib-induced hypertension and myocardial injury.

The patient in this report was quite elderly for a patient being treated with anti-cancer drugs. Thus, the patient’s vascular resistance and cardiac function were likely to be influenced by aging and may have been impaired before the sunitinib initiation. This may be why the alterations of arterial stiffness and cardiac function were easily induced by sunitinib initiation. Further studies using both the CAVI and echocardiography are needed to examine the timing of the appearance of sunitinib-induced cardiovascular effects in various age strata.

In conclusion, the increased arterial stiffness and abnormalities of cardiac functional parameters may precede the appearance of sunitinib-induced hypertension. Arterial stiffness assessed by the CAVI and echocardiography-derived cardiac functional parameters may be useful for the early detection of sunitinib-induced hypertension.

References


