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ORIGINAL ARTICLE

Impaired coronary flow reserve in metastatic cancer patients treated with sunitinib

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Summary

Purpose: *Hypertension is one of the major side effects of sunitinib, an angiogenesis inhibitor used in the treatment of metastatic renal cell carcinomas (mRCC) and gastrointestinal stromal tumors (GIST). Endothelial dysfunction, an early and reversible event in the pathogenesis of atherosclerosis, is suggested to be one of the possible underlying mechanisms of hypertension caused by angiogenesis inhibitors. Coronary flow reserve (CFR) measurement by trans-thoracic Doppler echocardiography (TTDE) reflects coronary microvascular and endothelial functions, as a cheaper and an easy screening test. We have used TTDE to evaluate endothelial function and coronary microvascular function in mRCC and GIST patients under sunitinib treatment.*

Methods: *Eighteen metastatic cancer patients (16 mRCC and 2 GIST) on sunitinib treatment and 27 healthy subjects were enrolled in this cross-sectional study. Thyroid stimulating hormone (TSH), lipid profile, creatinine, hemoglobin, glucose, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anthropometric and physical parameters of patients were recorded. CFR recordings were performed by the Vivid 7 echocardiography device.*

Results: *CFR was significantly lower in patients when compared with controls (1.82±0.4 vs 2.71±0.8, respectively; p < 0.001). Impaired CFR was found in 13 (72%) patients whereas all controls had normal CFR values. CFR was inversely correlated with the duration of sunitinib treatment (r=-0.36, p =0.01), high sensitivite (hs) CRP (r = -0.574, p = 0.01) and ESR (r = -0.5, p = 0.02).*

Conclusion: *Our findings indicate that CFR is significantly impaired in cancer patients on sunitinib treatment. There is an inverse correlation between CFR and duration of sunitinib treatment and inflammation markers.*

Key words: *cancer, coronary flow reserve, sunitinib, transthoracic Doppler echocardiography*

Introduction

Introduction of targeted therapies including sunitinib and sorafenib has resulted in an important improvement in the outcome of certain metastatic cancers such as RCCs and GISTs. Targeted therapies are effective with acceptable side effects compared to traditional chemotherapy or immunotherapy. Recently, however, cardiotoxicity has beeen reported to be a potentially important side effect of small-molecule tyrosine kinase inhibitors (TKIs) [1].

Sunitinib malate is a member of TKIs, along with vascular endothelial growth factor receptor (VEGFR) type 1 and type 2 (FLT1/KDR), platelet derived growth factor receptors (PDGF-α, PDGF-β), stem cell factor receptor (c-KIT) and FLT3 and RET kinases. TKIs inhibit normal variants of tyrosine kinases in noncancerous cells, which can lead to toxic effects affecting the cardiovascular system. Hypertension is one of the most common side effects. Hypertension induced by anti-angiogenic drugs is probably related to an increase in

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systemic vascular resistance. The vascular rarefaction (decrease in the density of microvessels) and endothelial dysfunction is one of the major mechanisms resulting in systemic vascular resistance [2-5]. It is reported that there were not many significant changes in the humoral factors in the TKIs-treated patients experiencing hypertension [6]. Thus, impaired angiogenesis or endothelial dysfunction is supposed to be the cornerstone mechanism of elevated blood pressure.

Endothelial dysfunction is an early step in the development of atherosclerosis and contributes to the formation, progression and complication of atherosclerotic plaque. It is mainly characterised by a reduction in the bioavailability of nitric oxide (NO). A number of studies have demonstrated that asymptomatic patients with cardiovascular risk factors may be affected by endothelial dysfunction. The impaired response to endothelial vasodilators such as acetylcholine and bradykinin indicates endothelial dysfunction [7].

CFR represents the capacity of the coronary circulation to dilate following an increase in myocardial demands. Although CFR was used to be measured invasively until recently, CFR has been evaluated in echo-lab recently by using Doppler and vasodilator such as dipyridamole or adenosine [8]. This method provides evaluation of CFR before angiographically detectable stenosis develops in epicardial coronary arteries. Thus, early coronary microvasculature pathology could be investigated [9].

The aim of this study was to investigate the circulation of coronary microvessels and endothelial function of epicardial coronary arteries by measuring CFR using TTDE, in patients with metastatic RCC or GIST under sunitinib treatment.

Methods

Patients and healthy controls

Between April 2006 and January 2011, 79 patients received second-line sunitinib therapy for mRCC at our institution. Sunitinib was administered at a dose of 37.5 mg daily without interruptions and was withdrawn after patient request or due to severe toxicities. During this study, only 49 patients were alive. Eighteen of them were excluded based on exclusion criteria, 4 patients refused to participate in the study, and 9 patients started sunitinib very recently, making them immature for CFR evaluation. Thus, only 18 patients were enrolled in the current study. Five patients with GIST received sunitinib 37.5 mg/day. Two of these 5 GIST patients did not accept to be included into this study and one patient had already ischemic cardiovascular disease, thus he was not included into the study.

Twenty-seven sex- and - smoking history-matched healthy controls were recruited from hospital staff and friends. The control subjects were all nondiabetic without any discernible risk factor other than arterial hypertension for the development of impaired CFR.

Inclusion criteria

1. Diagnosis of mRCC or metastatic GIST patients receiving sunitinib for at least 3 months.
2. No established cardiovascular disease; no overt clinical evidence of atherosclerotic cardiovascular disease.
3. Normal thyroid function tests.
4. Written informed consent.

Exclusion criteria

1. mRCC or GIST patients not treated with sunitinib or received sunitib for less than 3 months.
2. Established cardiovascular disease, with overt clinical evidence of atherosclerotic cardiovascular disease. Other chronic diseases that accelerate atherosclerosis, such as diabetes mellitus and hyperlipidemia. Controlled essential hypertension was not an exclusion criterion.
3. Abnormal thyroid function tests.
4. Not giving written informed consent.

Ethical approval for the study was obtained from the Instutional Ethics Commitee and each subject gave written informed consent to participate in the study.

Biochemical, anthropometric and physical parameters

All biochemical analyses including serum glucose, total cholesterol, plasma triglyceride (TG) concentrations, hemoglobin, creatinine, CRP, and ESR were retrieved from the patient medical records.

Body mass index (BMI) was calculated as the ratio of weight (kg) divided by height (cm) squared. Systolic and diastolic blood pressures were measured on the right arm of subjects in an upright sitting position after at least 5 min of rest using a sphygmomanometer with appropriate cuff size. Two readings were recorded for each individual. The average of 2 readings was defined as the subject's blood pressure (BP).

Coronary flow measurement

A single investigator (H.O.) measured the coronary flow velocity. The intra-observer variability of CFR measurement was 3.9% in the current study. The Vivid 7 echocardiography device (General Electric, USA) with a middle-range frequency (3-8 MHz) broadband transducer was used for CFR recordings.

The CFR was evaluated in the left anterior descending (LAD) coronary artery with TTDE. In the left lateral decubitus position, around the midclavicular line in the fourth and fifth intercostal spaces was the

Table 1. Laboratory data in patients and controls (average ± standard deviation)

Laboratory data	*Control subjects*	*Patients treated with sunitinib*	*p-value*
Total cholesterol (mg/dl)	171±19	156±32	0.015
Triglyceride (mg/dl)	118±34	116±44	NS
Fasting blood glucose (mg/dl)	83±8	110±8	<0.001
Creatinine (mg/dl)	0.9±0.1	1±0.9	NS
Hemoglobin (g/dl)	13.8±1.65	12.9±2	0.018
TSH	1.6±1.2	1.95±0.9	NS
hs-CRP (mg/dl)	-	19±23	-
ESR (cm/h)	-	57±41	-

Hs-CRP: high sensitive C-reactive protein, ESR: erythrocyte sedimentation rate, TSH: thyroid stimulating hormone

acoustic window. The left ventricle could be imaged in the long-axis cross section. The ultrasound beam was laterally inclined. The color Doppler flow mapping guidance with the optimal velocity range (+12 to + 15 cm/sec) searched coronary blood in the mid-to-distal LAD. Then in the LAD artery, 1.5 - 2.0 mm wide sample volume was positioned on the color signal. The variables of LAD artery velocity were measured by using fast Fourier transformation analysis.

Dipyridamole (Persantin, Boehringer Ingelheim, 0.56 mg/kg) was infused over a 4-min period, after baseline recordings of coronary flow were completed. If a 10% increase from the baseline in the heart rate was not observed, additional dipyridamole (0.28 mg/kg over a 2-min period) was infused. The hyperemic spectral profiles in the LAD artery were recorded 2 min after the end of the infusion, The images were recorded for playback analysis and were later measured off-line. At baseline and under hyperemic conditions, the average diastolic peak velocity (ADPV) was measured (Figure 1 and 2). The ratio of ADPV at hyperemia: ADPV at baseline was defined as CFR.

All of the patients and controls were abstained from caffeine-containing drinks for at least 12 h before testing. The CFR was measured between 8 and 9 a.m. in all subjects.

Table 3. Coronary flow findings of control subjects and patients (average ± standard deviation)

Flow findings	*Control subjects*	*Patients treated with sunitinib*	*p-value*
Baseline ADPV (cm/s)	28±9.48	32.5±7.29	0.067
Hyperemic ADPV (cm/s)	68±29.77	55.5±15.29	0.04
CFR	2.5±0.81	1.68±0.4	<0.001
CFR < 2 (%)	15	72	<0.001

CFR: coronary flow reserve, ADPV: average diastolic peak velocity

Statistics

SPSS software (SPSS16, Chicago, IL, USA) was used for statistical analyses. Data were expressed as mean ± SD. Comparisons between controls and patients were carried out using the Student's t-test. Relationship between variables was calculated by simple correlation. Differences were considered significant when p-values were less than 0.05.

Results

Table 1 illustrates the metabolic data in both patients and controls. No significant differences were observed between patient and control groups with respect to plasma TG concentrations, creatinine and TSH levels. Patients who had been treated with sunitinib had significantly lower serum total cholesterol and hemoglobin levels compared to controls (p=0.015 and p=0.018, respectively). Serum fasting glucose levels were found to be higher in patients than those in controls (p<0.001).

Table 2. Clinical characteristics of patients and control subjects (average ± standard deviation)

Characteristics	*Control subjects*	*Patients treated with sunitinib*	*p-value*
Age, years (range)	43±7 (30-70)	53±12 (26-72)	0.001
Gender (male/female)	17/10	12/6	NS
Body mass index (kg/m^2)	27±3.6	26 ± 4.8	NS
Duration of sunitinib treatment, months (range)	-	12±9 (4-36)	-
Histology			
Renal cell carcinoma	-	16	-
Gastrointestinal stromal tumor	-	2	-
Systolic blood pressure (mmHg)	120±9	130±16	0.002
Diastolic blood pressure (mmHg)	70±6	80±8	0.002
Baseline heart rate (beats/min)	68±12	80±16	NS

NS: non significant

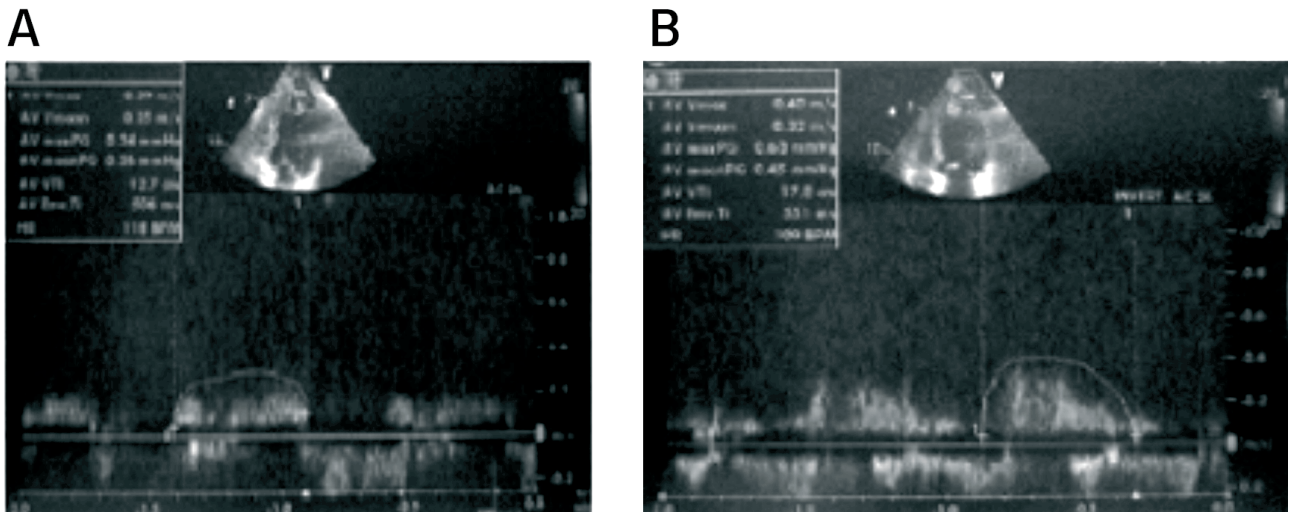

Figure 1. (**A**) Pulse-wave Doppler recording of blood flow (average diastolic peak velocity) in the left anterior descending coronary artery before dipyridamole infusion at baseline in a cancer patient under sunitinib treatment. (**B**) Pulse-wave Doppler recording of blood flow (average diastolic peak velocity) in the left anterior descending coronary artery after dipyridamole infusion during hyperemic condition in a cancer patient under sunitinib treatment.

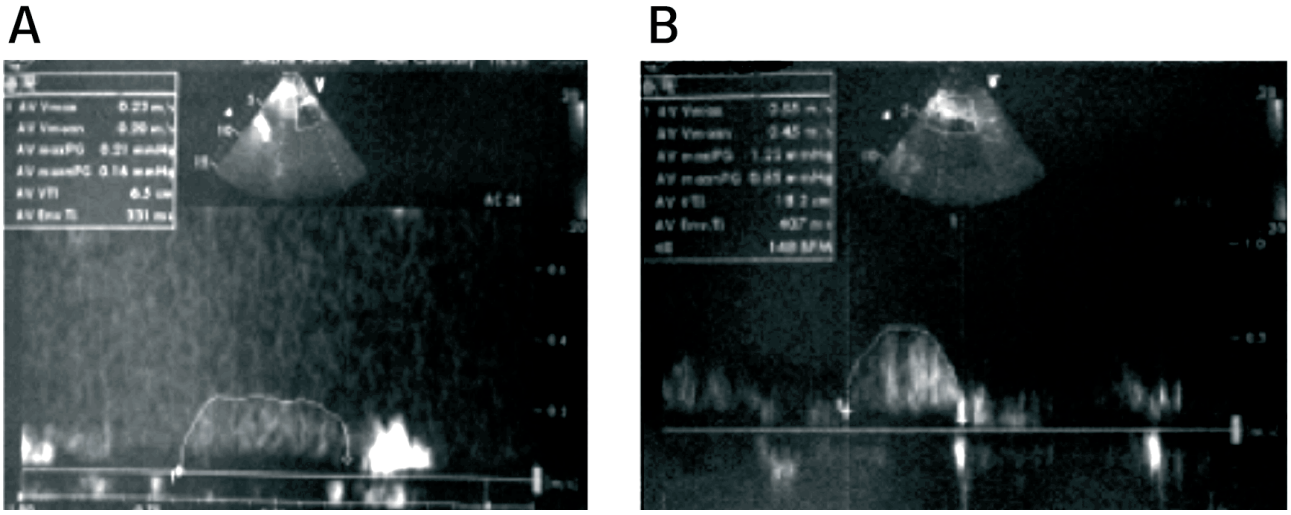

Figure 2. (**A**) Pulse-wave Doppler recording of blood flow (average diastolic peak velocity) in the left anterior descending coronary artery before dipyridamole infusion at baseline in a healthy control. (**B**) Pulse-wave Doppler recording of blood flow (average diastolic peak velocity) in the left anterior descending coronary artery after dipyridamole infusion during hyperemic condition in a a healthy control.

Table 2 illustrates the demographic, anthropometric and echocardiography data of the study group. Basal heart beat per min and BMI showed no differences between controls and patients on sunitinib treatment. CFR measurements are presented in Table 3. While ADPV-basal measurements in patients (Figure 1A) were similar compared with controls (Figure 2A), ADPV-hyperemia in patients (Figure 1B) were significantly lower than in controls (Figure 2B) (p=0.04). Impaired CFR was found in 13 (72 %) patients whereas all controls had normal CFR values. CFR values were significantly lower in patients than in controls (1.68±0.4;2.5±0.81, respectively, p<0.001) (Figure 3).

No significant correlations were observed between CFR and age, BMI, total cholesterol, plasma TG, creatinine, hemoglobin, and TSH. The CFR was inversely correlated with the duration of sunitinib treatment (r=-0.36, p=0.01), hs-CRP (r=-0.574, p=0.01) and ESR (r=-0.5, p=0.02) in the patient group. CFR was inversely correlated in fasting blood glucose levels (r=0.504, p≤0.001) in both patients and controls.

Discussion

Neovascularization is essential for cancer survival, local growth of cancer tissue, and for the development of distant metastases [10]. Angiogenic molecules secreted by cancer cells and

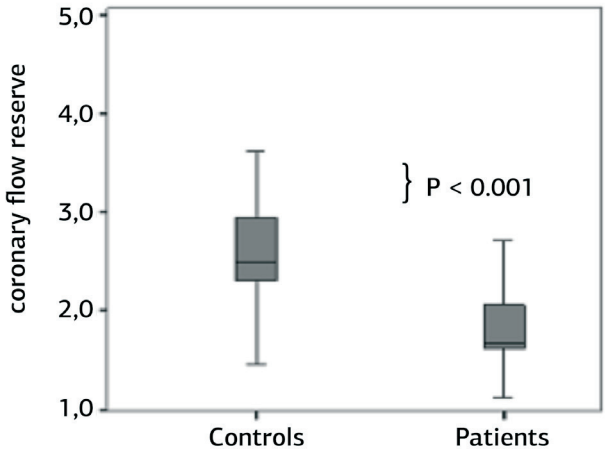

Figure 3. Coronary flow reserve measurements in controls and patients.

endothelial cells have key roles in neovascularization [11,12]. The effects of angiogenesis inhibitors on coranary microvasculature are not well known. In this study, we investigated whether the prolonged usage of sunitinib, one of the most important anti-angiogenic molecules in the treatment of RCC and GIST, disturbs the CFR.

VEGF stimulates endothelial cell proliferation by interaction with high-affinity receptor kinases, VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR), which are expressed on the surface of endothelial cells [13,14]. Other studies have shown that VEGF exerts its angiogenic effects by enhancing the transcriptional activity of endothelial NO synthase (eNOS) [15]. This finding suggests that VEGF may induce a hypotensive response. PDGF stimulates neovascularization by inducing VEGF production and modulating the proliferation of fibroblast-like cells and pericytes surrounding the endothelium [16,17]. Thus, in some solid tumors, particularly RCC and GIST, inhibition of vessel formation is thought to be the main mechanism to result in antitumor acitivity [18]. The Von Hippel Lindau hypoxia inducible (HIF-1)-related gene products are the main targets for sunitinib and are also physiologic mediators of myocardial response to acute or chronic ischemia, myocardial remodelling, peri-infarct vascularization and vacular permeability [19,20]. Sunitinib is a potent inhibitor of many angiogenic tyrosine kinases, especially VEGFR and PDGFR. Additionally, VEGF inhibition diminishes NO synthesis [21, 22].

The exact frequency of cardiotoxicity induced by anti-angiogenic treatment is unknown. In phase III trials, cardiovascular adverse events were usually identified after clinical symptoms occurred. Cardiovascular symptoms such as chest pain and palpitation are unreliable indicators in cancer patients. Recently, Schmidinger et al. reported the results of detailed cardiovascular monitoring during sunitinib or sorafenib treatment as they aimed to show early signs of myocardial damage [1]. Among 74 eligible patients, 33.8% experienced a cardiac event, 40.5% had ECG changes, 18% were symptomatic, and 9.4% were seriously compromised and required intermediate and/or intensive care admission. After cardiovascular management, such as medication, coronary angiography, pacemaker implantation and operation, all patients recovered. Sunitinib or sorafenib were continued in all patients. The authors concluded that cardiac injury under TKI treatment is a largely underestimated phenomenon, however as the first signs of myocardial damage appear, prompt careful cardiovascular monitorizing and cardiac treatment should be applied to patients, thus cardiac damage can become manageable and reversible.

It is known that the detection of endothelial function abnormalities in coronary arteries predicts future cardivascular events, but the new concept "coronary microvascular dysfunction" has been used to define a condition that often precedes the development of full-blown diseases and may have independent prognostic value [23]. Camici and Crea proposed that coronary microvascular dysfuntion can be classified in 4 groups (Type A-D) [24]. Type A occurs in the absence of coronary artery and myocardial diseases; type B developes in the context of cardiomyopathies; type C occurs in the presence of obstructive epicardial coronary artery disease and type D is iatrogenic. The CFR evaluation during dypiridamole stress echocardiography is a sensitive means of detecting epicardial stenosis and coronary microcirculatiom impairment [25]. The ratio between peak diastolic flow velocity at hyperemia (induced by dypiridamole infusion) and at rest is the easiest parameter to obtain, and most closely correlates with the CFR measured using a Doppler flow wire [26]. A CFR < 2 is generally considered abnormal [27]. In our study, CFR values of patients under sunitinib treatment were found be less than 2 (1.68±0.4) and negatively correlated with duration of sunitinib treatment.

A number of studies demonstrated that patients with essential hypertension may have abnormal CFR despite angiographically normal coronary arteries [28]. Arterial hypertension is a common side effect of inhibitors of sunitinib [29,30]. There are conflicting data about the mechanisms by which angiogenesis inhibitors

can increase blood pressure. Van der Veldt et al. investigated in mRCC patients whether sunitinib impairs microvascular function and induce capillary rarefaction. They assessed skin capillary density at baseline, after venous occlusion which represents the structural capillary density for 60s and 120s. They investigated the endothelium-dependent and endothelium-independent vasodilation of finger skin microcirculation by using laser Doppler fluxmetry that was combined with iontophoresis of acetylcholine and sodium nitroprusside. It was also demonstrated that visibility of subpapillary plexus increased during sunitinib treatment which was related with a decrease in capillary density, but sunitinib treatment was not related with impaired microvascular endothelium-dependent and endothelum-independent vasodilatation. Increasing the duration of venous occlusion did not result in any change in the number of visible capillaries [31,32]. However, reduced formation of NO by endothelial cells is caused by decreased responsiveness of vascular smooth muscle cells to NO and an increased production or reaction to vasoconstricting stimuli are suggested to result in arterial hypertension [33,34]. Although strict blood pressure control by regular assessment of arterial blood pressure and increasing the dose or number of antihypertensive drugs were performed to our patients and the control group was matched with the patient group in terms of history of hypertension, basal systolic and diastolic blood pressures of patients were found to be higher than those of controls. Thus, in our study it is difficult to conclude that increased blood pressure itself is only the cause of impaired CFR in these patients or impaired NO synthesis induces impaired CFR and arterial hypertension.

Atherosclerosis has been considered an inflammatory disease and the association of atherosclerosis with systemic autoimmune diseases has induced researches which investigate autoimmune mechanisms participitating in atherogenesis [35,36]. Many solid tumors secrete proinflammatory cytokines or stimulate inflammatory cells, thus resulting in inflammation. The increased expression of adhesion molecules and proinflammatory cytokines leads to abnormal endothelium-dependent vasodilation which could be investigated by TTDE as well. A correlation between CRP levels and atherosclerosis has been reported [37,38]. In this study, we revealed a negative correlation between the serum CRP levels and ESR. Increased proinflammatory cytokines may be another contributing factor in reduced CFR in our study population.

Although none of our patients was diabetic, fasting blood glucose levels were significantly higher in patients than in controls. Impaired glucose tolerance, but not impaired fasting glucose, is reported to be a risk factor for early-stage atherosclerosis [39]. We also found no relationship between fasting glucose levels and CFR measurements.

To our knowledge, this is the first report that analyses the effect of sunitinib treatment on the coronary blood flow, measured by a non-invasive method, TTDE. Cancer patients treated with sunitinib had lower CFR values and impairment of CFR increased with long duration of sunitinib treatment. These may be regarded as an early finding of an affected cardiovascular system and CFR measurement by TTDE can be used as a non-invasive screening test for cardiac evaluation of cancer patients under sunitinib treatment.

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