Case Report
Future Oncology

Role of preeclampsia-related angiogenic factors in sunitinib cardiotoxicity: two cases and review of the literature

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Sunitinib is a multi-targeted tyrosine kinase inhibitor widely used in clear cell renal carcinoma and in imatinib-resistant gastrointestinal stromal tumors. Sunitinib-associated cardiotoxicity has been recognized and includes hypertension, left ventricular dysfunction and congestive heart failure; nevertheless, few data exist in the literature regarding the role of preeclampsia-related angiogenic factors in sunitinib cardiotoxicity. We report a case of sunitinib-induced severe left ventricular dysfunction that occurred in a hypertensive woman with metastatic renal carcinoma and a history of preeclampsia, and a case of sunitinib-induced preeclampsia-like syndrome in a normotensive patient with an imatinib-resistant gastrointestinal stromal tumor. Our experience confirms that inhibition of angiogenic factors to treat cancer is a novel challenge for the oncologist and requires the cardiologist's support.

Cancer therapies have changed dramatically in recent years due to the development of targeted therapies, among which there is sunitinib, a tyrosine kinase inhibitor (TKI) whose targets include the VEGF receptor (VEGFR) and PDGF receptor (PDGFR) [1]. Sunitinib represents the reference treatment in patients with metastatic clear cell renal carcinoma (RCC) and with imatinib-resistant gastrointestinal stromal tumor (GIST) [1,2]. However, as reported in recent studies, TKI-related cardiotoxicity has become an emergent issue [3]. Here, a case of sunitinib-induced severe left ventricular dysfunction that occurred in a hypertensive woman with metastatic RCC and a history of preeclampsia, and a case of sunitinib-induced preeclampsia-like syndrome in a normotensive patient with an imatinib-resistant GIST are reported.

Case reports

First case: sunitinib-induced severe left ventricular dysfunction in a patient with a history of preeclampsia

A 51-year-old woman was admitted to the authors' hospital with abdominal pain in April 2009. She had suffered preeclampsia during her last pregnancy at the age of 35 years and had been hypertensive ever since. She was taking angiotensin receptor blockers and β-blockers. CT scans demonstrated a left renal mass with multiple liver metastases. The patient underwent left nephrectomy. Pathology demonstrated a RCC, grade 3, pT3bN2M1. One month later, the patient began oral sunitinib daily (50 mg for a 4-week-on, 2-week-off schedule). Her basal ECG was normal and her basal ejection fraction was normal, with a moderate septal hypertrophy of 14.8 mm and mild mitral regurgitation. While on sunitinib, she experienced progressive effort dyspnea. In the last week of her second 4-week-on cycle, she was referred for severe dyspnea. Her ECG showed ST depression and negative T waves in D1, aVL and V4–V6, her blood pressure was poorly controlled in spite of her usual therapy. Echocardiography showed ejection fraction reduction (approximately 35%) with global hypokinesis and moderate mitral regurgitation. A high sensitivity-troponin I increase to 0.16 ng/ml was also present (cutoff value in the authors' laboratory: 0.06 ng/ml). After discontinuation of sunitinib and the increase of dosage of angiotensin

Keywords
■ preeclampsia ■ sunitinib
■ TKI-induced cardiotoxicity

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receptor blockers and β-blockers, left ventricular ejection fraction (LVEF) improved to 55% with regression of heart failure symptoms. The patient died owing to progressive disease after a few months.

Second case: sunitinib-induced preeclampsia-like syndrome in a young normotensive patient

A 41-year-old woman had received distal gastrectomy in April 1993 for GIST. In March 2003 a CT scan showed multiple liver metastases. After the confirmation of metastatic GIST obtained by histological examination of a liver biopsy positive for CD117 and CD34, negative for S100, with a mitotic count 6/50 high power fields, oral imatinib (400 mg/day) was started. Disease progression occurred 60 months after therapy initiation, and imatinib was increased to 800 mg/day. After 10 months, due to further progression of liver disease, imatinib was discontinued and second-line therapy with sunitinib 50 mg daily, according to a 4-week-on, 2-week-off schedule, was started. After 2 weeks of sunitinib, the patient developed effort dyspnea, chest pain and hypertension. Her ECG showed negative T waves in V3 and V4. Neither troponin release nor systolic function abnormalities at echocardiography were present. She started antihypertensive therapy with perindopril 4 mg and carvedilol up to 12.5 mg twice a day. The ECG normalized during sunitinib washout. During subsequent challenges with sunitinib, further ECG abnormalities were observed (mostly in the third week of therapy), with normalization during washout. After 2 years of therapy, the patient developed a preeclampsia-like syndrome with hypertension, proteinuria (0.820 g/24 h; normal range: 0.0–0.165) and microalbuminuria (333.4 mg/24 h; normal range: 0–30). She needed to be treated with three antihypertensive drugs; perindopril 4 mg, carvedilol 25 mg and amlodipine 10 mg, daily. Currently, treatment with sunitinib is still ongoing with close monitoring of renal function and blood pressure, while the neoplastic disease is stable.

Discussion

'Targeted' therapeutics refer to drugs that inhibit the specific gene products that drive tumorigenesis. High mutation rates in protein kinases were found in cancer and these mutations were found 'causally' related to the tumor, playing a remarkable role in tumorigenesis. Sunitinib is a 'multi-targeted' agent that not only inhibits the mutated/overexpressed kinases driving cancer cells but also inhibits tumor angiogenesis, and this second function is achieved through inhibition of VEGFRs and, less commonly, PDGFRs [1]. Angiogenesis is a process in which endothelial cells (ECs) sprout from pre-existing blood vessels. The mechanism of angiogenesis is very closely regulated and VEGF plays an important role in this process [4,5]. In particular, VEGF interacts with two different receptor tyrosine kinases, VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1), to alter angiogenesis. Experiments have shown that VEGF has the ability to stimulate microvascular EC proliferation. VEGF is also capable of enhancing EC migration, inhibiting EC apoptosis and inducing the growth of new capillaries from pre-existing vasculature. VEGF is upregulated during hypoxic condition via a mechanism that involves hypoxia-inducible factor, a protein released during oxygen stress. The circulating form of the VEGFR-1 receptor, called the soluble fms-like tyrosine kinase receptor-1 (sFlt-1), opposes angiogenesis via a mechanism of binding and sequestering salutary VEGF ligands in the circulation with ensuing endothelial dysfunction and vascular rarefaction that increase pressure load on the heart. The other sunitinib target (PDGFR) increases capillary wall stability, stimulates the proliferation of cultured pericytes and smooth muscle cells, increases DNA synthesis on capillary ECs and stimulate formation of angiogenic sprouts *in vitro*.

Adverse events due to therapy with angiogenesis inhibitors include hypertension, proteinuria and thromboembolism. Preeclampsia patients overexpressing sFlt-1 show hypertension and proteinuria, suggesting a similar mechanism for the induction of these symptoms [5]. In particular, it is believed that trapping of VEGF with sFlt-1 may result in hypertension and proteinuria. However, as better explained later, the exact mechanisms of the VEGF-induced signaling pathways for the development of these adverse events are not entirely known.

Sunitinib-related cardiotoxicity may be explained by the disruption of multiple signaling pathways that are of pivotal importance in the maintenance of adult cardiac function. At least three key pathways have been causally related to sunitinib cardiotoxicity: AMP-activated protein kinase, PDGFRs and VEGFRs [6]. PDGFRs are expressed in cardiomyocytes and overexpression of PDGFRs can signal cardiomyocyte survival [7]. Inhibition of VEGFRs may explain the frequent occurrence of hypertension and this is a class effect of antiangiogenic agents [8].

Small molecule kinase inhibitors, such as sunitinib, block phosphotransferase activity competing with ATP for binding to the ATP pocket. The structure of the ATP pocket is highly conserved across the many kinases of the human genome (more than 500). It is easy to inhibit a kinase of interest but this lack of selectivity causes so-called 'off-target' effects (the inhibition of a kinase not intended to be inhibited) and, if the kinase plays a critical role in the heart, the off-target toxicity may lead to cardiotoxicity. Kinase inhibitors that target essential kinases in the heart and vasculature are likely to cause cardiotoxicity. As Force and Cheng pointed out, there are two types of toxicity: 'on-target' toxicity (also called mechanism-based) and off-target toxicity; this second effect accounts for cardiotoxicity [9,10]. As far as sunitinib is concerned, this drug leads to significant hypertension and this increased cardiac load does play a role in left ventricular dysfunction, but a contributory role rather than a causal one. Mechanisms of cardiotoxicity have been studied in cultured cardiomyocytes and they are related to energy compromise; off-target inhibition of AMP-activated protein kinase contributes to cardiotoxicity and this is an example of a kinase inhibition that is useful for tumor cell killing, but is also important for metabolic homeostasis in the heart. It is not completely defined whether the myocardial damage is due to myocyte loss (and therefore irreversible) or myocyte dysfunction (potentially reversible). The normalization of TKI-induced left ventricular dysfunction after withdrawal of drug and institution of heart failure therapy (ACE-inhibitors, angiotensin receptor blocker or β-blockers) make the type II cardiotoxicity more likely. Cardiotoxicity from cancer drugs has been classified by Ewer and Lippman; the authors identified drugs such as anthracyclines that have the potential to cause irreversible damage (type I cardiotoxicity) versus drugs such as trastuzumab that predominantly induce reversible dysfunction (type II cardiotoxity) [11]. In type I cardiotoxicity, myocyte injury has been demonstrated in specimens from endomyocardial biopsies and by troponin release. Cardiac biopsies from patients treated with trastuzumab and sunitinib did not show major myocardial injury, therefore sunitinib-induced myocardial damage should represent a type II cardiotoxicity. The limitations of this classification have been observed with trastuzumab, a typical type II drug, that can cause irreversible cardiac damage with troponin release in patients with severe pre-existing cardiac disease or after anthracycline therapy. Even the reversibility of antiangiogenic drugs has not been completely proven. Cases of reversibile myocardial dysfunction occurring in patients treated with sunitinib have been reported in the literature [12,13]. However, recent observations have questioned the reversibility of sunitinib-induced left ventricular dysfunction. In addition, sunitinib can induce myocyte apoptosis in preclinical models.

The precise rate of cardiotoxicity associated with TKIs is unknown; in fact, Phase III trials have not pursued cardiac end points, and the identification of cardiac adverse effects was predominantly based on the occurrence of clinical symptoms [14]. In the randomized trial published by Motzer *et al.*, in which sunitinib was compared with IFN-α in patients with previously untreated metastatic RCC, a 10% decline in LVEF was observed, with a median time to cardiovascular events of 30.5 weeks [1]. However, updated cardiotoxicity data indicated that 15% of patients treated with sunitinib developed symptomatic grade 3/4 heart failure [15]. In a large Italian study the cardiovascular toxicity of 175 patients with metastatic RCC treated with sunitinib at eight institutions, including the current authors' center, was retrospectively reviewed [16]. The major finding of this study was that 9.7% of patients developed grade 3 hypertension, 18.9% developed grade 1–3 LVEF dysfunction and 6.9% developed congestive heart failure (Table 1). In 75 imatinib-resistant GIST patients treated with sunitinib, Chu *et al.* reported an 11% incidence of cardiovascular events, including one myocardial infarction (1%) and six symptomatic heart failures (8%). In 36 patients treated at the approved sunitinib dose, a 28% incidence of absolute LVEF reduction of at least 10% and a 19% incidence of a LVEF reduction of 15% or more was observed. In this subset of 36 patients a 47% incidence of hypertension was also recorded, with a 17% incidence of grade 3 hypertension (Table 1) [17].

In this study, 75% of patients with a history of coronary artery disease had a sunitinib-induced cardiovascular event versus 7% of patients without prior coronary events. Endomyocardial biopsies showed swollen mitochondria, cardiomyocyte hypertrophy, release of cytochrome C into the cytosol and activation of caspase-9 leading to cell death. Troponin I was moderately increased in 18% of patients [17]. In another retrospective study on patients with metastatic renal cancer and imatinib-resistant GIST, 2.7% of patients

Table 1. Incidence of sunitinib-induced cardiotoxicity in three retrospective studies.

Study (year)	Patients (n)	Grade 3 hypertension (%)	Grade 1–3 LVEF dysfunction (%)	CHF (%)	Ref.
Di Lorenzo *et al.* (2009)	175	9.7	18.9	6.9	[16]
Chu *et al.* (2007)	75[†]	17.0	28.0	8.0	[17]
Telli *et al.* (2008)	48	NR	NR	15.0	[15]

[†]36 patients were evaluated for hypertension and LVEF dysfunction.
CHF: Congestive heart failure; LVEF: Left ventricular ejection fraction; NR: Not reported.

developed heart failure (mean onset 22 days after initiation) with a decline in cardiac function and elevation in blood pressure [18].

Few data exist in the literature regarding the role of preeclampsia-related angiogenic factors in sunitinib cardiotoxicity. Preeclampsia, a pregnancy-specific syndrome characterized by new onset hypertension and proteinuria, may predispose to increased risk of hypertension and cardiovascular and renal disease [19]. The etiology of preeclampsia is unclear, but recent studies seem to suggest that hypertension and proteinuria are based on widespread maternal endothelial dysfunction and microangiopathy. There is evidence that an excess of antiangiogenic factors, most notably sFlt-1 and soluble enoglin, mediates symptoms and signs of preeclampsia. sFlt-1 can bind to the angiogenic growth factors VEGF and PGFR, neutralizing their function and causing endothelial dysfunction and proteinuria. Excess placental sFlt-1, the extracellular domain of VEGFR, and low concentration of free VEGF and free PGF have been observed during and prior to clinical manifestation of preeclampsia [20,21].

Many modulators of vascular receptors have been implicated as possible biologically active factors in preeclampsia [22]. Many markers of endothelial dysfunction have been reported in women with preeclampsia with increased circulating endothelin-1 (ET-1) levels. In rats treated with the VEGFR inhibitor, Kappers *et al.* found a reversible rise in blood pressure and plasma ET-1, proteinuria and marked renal histologic abnormalities; findings that resemble those found in preeclampsia [23]. A preeclampsia-like syndrome does occur in patients undergoing treatment with angiogenesis inhibitors, including the multi-targeted kinase inhibitor sunitinib [24]. Kappers *et al.* also demonstrated a reversible rise in blood pressure associated with activation of the ET-1 system, suppression of the renin–angiotensin system and generalized microvascular dysfunction in patients with metastatic RCC or GISTs treated with sunitinib [23]. In these cases, patients are observed to have antiangiogenic-induced hypertension, which may be accompanied by proteinuria and/or other symptoms of preeclampsia. In a more recent paper, Kappers *et al.* showed that both the ET-1 system and oxidative stress may be involved in sunitinib-induced proteinuria, whereas the ET-1 system is more important than the oxidative stress in sunitinib-induced hypertension [25]. As we have already pointed out, Nagai *et al.* analyzed the similarities between preeclampsia and VEGF-targeted therapy-induced hypertension and concluded that the hallmark of preeclampsia is similar to the toxicities related to antiangiogenesis therapy [5].

Since VEGF and its mediators play a pivotal role in the regulation of angiogenesis, angiogenesis inhibitors targeting the VEGF signaling pathways have adverse effects including hypertension, proteinuria and thromboembolism. Hypertension and proteinuria are indeed observed in preeclampsia patients overexpressing sFlt-1; the soluble tyrosine kinase receptor opposes angiogenesis through a mechanism of binding VEGF ligands and VEGFR is the final target. This common pathway between preeclampsia and antiangiogenesis-induced hypertension can explain the impressive cardiac adverse effect in the first described patient: an endothelium with disrupted signaling between antiangiogenic growth factors may have overreacted to the administration of an antiangiogenic agent with a redundant response (uncontrolled hypertension and severe congestive heart failure). In this case, the effect of the antiangiogenic agent was indeed enhanced by the fact that the patient's endothelium had been somehow 'primed' by the previous inhibitory action of sFlt-1 during preeclampsia

and that the addition of the antiangiogenic effect of sunitinib was superimposed on a damaged endothelium. sFlt-1 is indeed a mediator of both sunitinib action and endothelial dysfunction in preeclampsia. Moreover, the reduced capacity of the patient's hypertrophied left ventricle made it incapable of coping with an increased load such as the uncontrolled hypertension. The loss of compensatory factors in a stressed ventricle, through PDGFR and VEGFR inhibition, contributed to the severe left ventricular dysfunction. PDGF-β signaling is an important aspect of heart development. It has also long been known that PDGF may play a role in the restructuring of the fetoplacentar vasculature, in particular when there is inflammation of the vascular intimal layer [26].

Unfortunately the authors could not measure endothelin level or other angiogenic factors such as VEGF, BFGF or sFlt-1 in the first patient. In the second case reported, the patient, while on sunitinib, developed severe hypertension, effort dyspnea and ST-T abnormalities, but the myocardium and the endothelium of this patient were 'naive' to angiogenic factors and the left ventricle could cope with the increased load with no myocyte loss. Cases of sunitinib-induced preeclampsia-like syndrome are indeed documented in preclinical studies with the induction of high circulating levels of sFlt-1, and this observation confirms the assumption that the VEGFR block may have a pathogenic role in both preeclampsia-induced and antiangiogenic-induced endothelial dysfunction.

Cardiovascular disease and preeclampsia also share many risk factors and pathophysiological abnormalities, such as hypertension, insulin resistance and increased systemic inflammatory response.

There are also reports that antiangiogenic-induced hypertension is more severe in patients with renal carcinoma.

These findings should make us more careful when selecting patients for an antiangiogenic treatment, especially hypertensive patients. From patient's history we may understand whether or not the patient's endothelium has been either damaged by previous noxae or disrupted in its signaling pathways (as in our first patient) and we may better tailor antiangiogenic therapy.

In order to detect and treat TKI-related cardiotoxicity, oncologists and cardiologists have to work together. When an antiangiogenic therapy is planned, the oncologist should refer the patient to the cardiologist, but from that moment on it is the cardiologist's responsibility to define the intrinsic cardiologic risk of the single patient and to evaluate the potential cardiotoxicity of the TKI in that patient. If hypertension is present, it is the cardiologist's duty to optimize therapy, if other risk factors are present it is once more the cardiologist who has the responsability to reduce the burden of diabetes or dyslipidemia on the endothelium, and to discourage smoking.

On the other hand, the decision to reduce the dosage of TKIs or to modify the schedule of administration of TKIs is the oncologist's responsibility.

While on TKI therapy, early recognition of cardiovascular side effects is mandatory to allow long-term continuous treatment with these agents. In addition, since a preeclampsia-like syndrome can occur in these patients, proteinuria and microalbuminuria should be closely monitored; in these patients it would be useful to also measure circulating levels of endothelin and sFlt-1. It may be that the use of biomarkers such as troponin and brain natriuretic peptide can help in early diagnosis of cardiotoxicity.

Cardiologists and oncologists should realize that long-term follow-up is particularly important in patients treated with kinase inhibitors because, as opposed to traditional chemotherapies, therapy with kinase inhibitors is often taken for long periods of time.

We may end up stating what van Heeckeren said about the new vascular disrupting agents that: "It is time for oncologists to engage cardiologists when dealing with vascular anticancer agents", but we would rather say, as McMullen did: "mind the heart" while treating patients with new anticancer agents [27,28]. However, cardiologists, too, have to learn many lessons from 'targeted therapies': the unexpected triggers of heart failure and the recent awareness that specific paracrine ligand–receptor interactions are indispensable for normal cardiac performance have uncovered an 'up-to-date' heart that, according to Brutsaert, is a pluricellular tissue pump in which cross-talk between different cell types and structural components contributes to ventricular homeostasis [29]. Unfortunately, this pluricellular paracrine organ is vulnerable when these intracellular networks are interrupted by targeted drugs. In this scenario of unexpected interactions a cardio-oncology team seems to be the best option throughout the journey of the patient in cancer treatment. As Suter and Ewer recently said: "The vital balance of accepting temporary cardiovascular side effects so as not to impede a patients' ability to benefit from cancer treatment is a fundamental component of a new

discipline now often referred to as cardio-oncology or onco-cardiology" [30].

Future perspective

The inhibition of angiogenic factors to treat cancer is a novel challenge for the oncologist and requires the cardiologist's support. In particular, while on sunitinib therapy, early recognition of cardiovascular side effects is mandatory to allow long-term continuous treatment with this agent.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Sunitinib-associated cardiotoxicity is recognized and includes hypertension, left ventricular dysfunction and congestive heart failure.
- Few data exist in the literature about the role of preeclampsia-related angiogenic factors in sunitinib cardiotoxicity.
- The reported cases show that patients with an indication for sunitinib should be carefully screened for a history of preeclampsia, as well as for other signs and factors that might predispose to hypertension.

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