Aortic dissection in a patient treated by sunitinib for metastatic renal cell carcinoma

The development of antiangiogenic agents targeting the vascular endothelial growth factor (VEGF) pathway (sunitinib, sorafenib, bevacizumab and temsirolimus) has revolutionized the treatment of metastatic renal clear-cell carcinoma. Adverse events attributed to these agents targeting the vascularization include cardiovascular effects. We report here a case of aortic dissection in a patient treated by sunitinib and discuss the cardiovascular toxicity of sunitinib.

The diagnosis of kidney cancer with lung metastasis was retained in a 58-year-old man. The patient underwent first a radical nephrectomy. The pathological examination classified the tumor as pT3b pN2 M1-type II papillary renal cell carcinoma. A history of pre-existing hypertension controlled by nebivolol was noted, without any other comorbidities. Medical treatment was begun with sunitinib at the classical schedule. The clinical tolerance was initially good, as the blood pressure monitoring. During the fourth cycle, the patient experienced episodes of moderate thoracic pain but did not seek medical advice. The scheduled computed tomography scan carried out after the end of the fourth cycle revealed the apparition of a distal (type B) aortic dissection (Figure 1), with progression of lung metastases. Sunitinib was thus discontinued. The thoracic surgeon advised against surgery. Addition of a new antihypertensive drug was required. The patient was then treated with temsirolimus.

This is the first aortic dissection case in a patient treated with sunitinib. At American Society of Clinical Oncology 2008 annual meeting, Aragon-Ching et al. [1] reported a case of aortic dissection in a patient included in a phase II trial of docetaxel, thalidomide and bevacizumab combination for metastatic castration-refractory prostate cancer.

Aortic dissection generally occurs in patients with predisposing factors: hypertension, atherosclerosis, diabetes and Marfan syndrome [2]. Hypertension is the most common predisposing factor for aortic dissection and is also a well-known adverse event of sunitinib. Proximal acute aortic dissection (type A) is a surgical emergency, whereas descending aortic dissection (type B) can often be treated medically.
Sunitinib and other treatments targeting the VEGF pathway have known cardiovascular adverse events. The most common is the development or the worsening of hypertension [3]. Some authors have proposed continuous monitoring of blood pressure, highlighting the high incidence of increase of blood pressure during treatment [4].

Clinically, the focus was initially placed on hemorrhagic events because of the potentially fatal outcome, but recent concern has also appeared about the cardiotoxicity of sunitinib, which may have been underestimated in clinical trials [5].

The pathogenic mechanism of sunitinib-induced cardiovascular toxicity remains poorly understood. Targeting both VEGF and platelet-derived growth factor (PDGF) receptors, sunitinib interferes with the normal functions of these growth factors. VEGF’s role in the formation of normal vessels during embryonic development is well studied, but its function in adults is unclear. PDGF plays a role in microvascularization stability by acting on pericytes and is also involved in blood vessels tonus. Inhibition of these two factors may affect vascular stability, although there is no data on sunitinib toxicity on pericytes similar to the toxic effect described by Chu et al. [5] on cardiomyocytes.

This case illustrates the importance of constantly monitoring the use of new drugs, even after official approval. Clinicians should consider treatment with antiangiogenic drugs as a cardiovascular risk factor.

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disclosure

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Figure 1. Computed tomography scan coronal reconstruction showing aortic dissection.

references


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