Acute aortic dissection during sorafenib-containing therapy

Sorafenib (BAY-43-9006, Nexavar®; Bayer Pharmaceuticals Corp., Wayne, NJ, and Onyx Pharmaceuticals Inc., Emeryville, CA)
CA), an orally bioavailable small-molecule receptor multikinase inhibitor, decreases tumor cell proliferation by inhibiting mainly the platelet-derived growth factor receptor and the vascular endothelial growth factor (VEGF) receptors. Sorafenib is approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma as a single drug at the dose of 400 mg twice daily. Usually well tolerated, hypertension arises as one of the major side-effects, with an overall incidence of 23.4%. Incidence of National Cancer Institute—Common Terminology Criteria for Adverse Events grades 3 and 4 hypertension ranges from 2.1% to 30.7% [1].

We report on a 77-year-old woman, with stage IV renal cell carcinoma, treated in a phase II clinical trial with the combination of gemcitabine 1000 mg/m² (days 1, 8), capecitabine 650 mg/m²/12 h (days 1–14) and sorafenib 400 mg twice daily each 3 weeks. She was admitted to our emergency department after the third cycle of treatment with severe acute epigastric pain and fatigue that had begun in the previous 4 h. No disease history was reported. Blood pressure of 200/106 was the unique finding at physical examination. Blood analysis, serum chemistries and electrocardiogram remained unremarkable. Computed tomography scan of the chest revealed a penetrating aortic ulcer with intramural hematoma in the descending thoracic aorta (Figure 1A). After 3 h of i.v. labetalol infusion and analgesic measures, a complete resolution of her symptoms as well as normalization of the blood pressure was observed. Good blood pressure was thereafter reached with three-drug combinations: a beta-blocker, an angiotensin-converting enzyme inhibitor and a diuretic. Sorafenib was withdrawn, following treatment with capecitabine and gemcitabine.

Possible mechanisms underlying the development of essential hypertension in these patients include impaired angiogenesis at the microcirculation level, endothelial dysfunction associated with decreased levels of the VEGF-stimulated vasodilator nitric oxide and changes in neurohormonal factors of the renin–angiotensin–aldosterone system [2]. However, Veronese et al. [3] demonstrated in 20 patients treated with sorafenib lack of significant change in either humoral factors or VEGF levels. Moreover, the authors described a sustained systolic blood pressure increase of ≥20 mmHg in 12 of 20 patients within the therapy, a high frequency if compared with that previously observed, probably because monitoring of blood pressure was stricter in this study. Additionally, sorafenib is more likely to develop hypertension during the drug initiation [3].

To our knowledge, only one case of acute aortic dissection has been described in a patient treated with bevacizumab therapy [4]. No reports during small-molecule inhibitor therapy have been published.

Since patients included in the prehypertension category (systolic blood pressure from 120 to 139 mmHg and/or diastolic blood pressure from 80 to 89 mmHg) suffer higher incidence of both cardiac and vascular events [5] and acute aortic dissection is a life-threatening medical emergency associated with high rates of morbidity and mortality, clinicians must be aware of this complication and tighter grading and closer surveillance of blood pressure is hence highly recommended.

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Figure 1. Descendent thoracic aortic dissection with a penetrating ulcer and intramural hematoma after 9 weeks of treatment (A), not observed in computed tomography scan at baseline (B).