Hypertension and proteinuria: a class-effect of antiangiogenic therapies

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Antiangiogenic therapy has now become a cornerstone in the treatment of several solid tumor cancers. Those drugs present with a renal toxicity profile manifesting as proteinuria and hypertension, often reported in the literature to be linked to bevacizumab, a monoclonal antibody targeted at the circulating vascular endothelial growth factor (VEGF). However, there is evidence that those side effects are most probably related to the pharmacological action of those drugs: the inhibition of the VEGF pathway. Thus, they may occur with any antiangiogenic therapy, either those acting on circulating VEGF (bevacizumab or VEGF-trap), or those acting on VEGF receptor(s) (sunitinib, sorafenib, or axitinib). Clinicians should thus be aware of such a 'class effect' to appropriately monitor and treat their patients, regardless of which antiangiogenic drug is used.

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Hypertension and proteinuria were first described with bevacizumab, a monoclonal antibody that targets the circulating vascular endothelial growth factor (VEGF). A recent meta-analysis by Zhu *et al.* [1] reported that the relative risk for proteinuria was 1.4 with bevacizumab at a low dose (3, 5, or 7.5 mg/kg/dose) and 2.2 at a high dose (10 or 15 mg/kg/dose). The relative risks for hypertension were 3.0 and 7.5, for the same ranges of doses. Eremina *et al.* [2] reported data on the mechanism of bevacizumab-induced thrombotic microangiopathy. They demonstrated that the inhibition of VEGF in the kidney leads to renal lesions the phenotype of which was similar to that of mice with a genetic loss of VEGF in the kidney. Recently, low molecular weight molecules that directly inhibit the tyrosine kinases on VEGF receptors have been marketed. Sunitinib was the first to be released, and several other tyrosine kinase inhibitors are being developed (sorafenib, axitinib, etc.). In clinical trials, sunitinib has been reported to induce hypertension in 30% versus 4% of metastatic renal cell carcinoma patients, and in 15% versus 11% of gastrointestinal stromal tumor patients [3]. A recent publication reported seven cases of proteinuria and hypertension in patients who received either sunitinib alone (four patients) or sorafenib followed by sunitinib (two patients). One patient was treated with sorafenib alone and developed proteinuria but no hypertension [4]. A potential class effect was suggested by those researchers and others [4,5]. We would like to point out that, according to in-vitro and in-vivo animal studies, there is evidence that those side effects most probably result from the inhibition of the VEGF pathway. Those side effects have been shown to be similar to preeclampsia. This disease, which occurs during pregnancy, is characterized by hypertension and proteinuria and renal thrombotic microangiopathy. It is also associated with high circulating levels of an endogenous inhibitor of VEGF signaling (soluble fms-like tyrosine kinase 1) [6].

The toxicity profile of antiangiogenic drugs is thus independent of their mechanism of action or their target, circulating VEGF or VEGF receptors. Moreover, the nature of the molecule, either large or small, has no influence on its toxicity and clinical evidence is emerging with all antiangiogenic drugs: bevacizumab, sunitinib, sorafenib, axitinib, or the more recent aflibercept (VEGF-trap) [5], a soluble recombinant decoy that binds to circulating VEGF [7–21] (Table 1).

Indeed, such a class effect, depending on neither the nature of the molecule nor its mechanism of action, would not be the first case in the history of targeted therapies. Cetuximab, gefitinib, erlotinib, and panitumumab, which all act on the epidermal growth factor pathway, share the same cutaneous toxicity profile. Cetuximab and panitumumab are monoclonal antibodies, whereas gefitinib and erlotinib are low molecular weight tyrosine kinase inhibitors. They all present with the same pattern of dermatological side effects [8].

It thus seems that agents acting on the same pathway may share similar toxicity profiles. Such toxicities may be observed whatever the nature or the target of the agent. As a result, we would like to emphasize that

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Table 1 Renal side effects of antiangiogenic therapies

Drug	Renal side effect	Prevalence/relative risk	References
Bevacizumab	Proteinuria	23–64%/1.4–2.2	[1]
	Proteinuria more than 3.5 g/day	6.5%	[9]
	Cryoglobulinemic glomerulonephritis or membranoproliferative glomerulonephritis (confirmed on renal biopsy)	Two cases	[10,11]
	Hypertension	11–36%/3.0–7.5	[1,9,12]
	Acute interstitial nephritis	One case	[13]
	Thrombotic microangiopathy	One case	[14]
	Thrombotic microangiopathy + IgA nephropathy	One case	[15]
Sunitinib	Hypertension	18%	[16]
	Hypertension	14 cases	[17]
	Thrombotic microangiopathy	One case	[14]
	Proteinuria	Six cases	[4]
Sorafenib	Hypertension	43–75%	[18,19]
	Acute interstitial nephritis	One case	[20]
	Proteinuria	One case	[4]
Axitinib	Hypertension	50–100%	[21]
	Proteinuria	23–70%	

proteinuria and hypertension should be considered as a class effect of all antiangiogenic therapies. Every cancer patient receiving such a drug should be closely monitored for hypertension and proteinuria, and treated when necessary. In the case of toxicity, there are no data on the potential benefit of switching from one drug to another. Prospective clinical studies, however, are needed to further investigate the toxicity profiles of those drugs, as they may be similar in nature, but different in incidence.

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