Angiogenesis is a key feature in the development and progression of malignancy, and antiangiogenic therapies are now well established as a cornerstone in the treatment of several cancers. Vascular endothelial growth factor (VEGF) not only drives angiogenesis but also acts as a survival factor for endothelial cells and promotes the abnormal phenotype of blood vessels in malignancy. By contrast, the healthy adult vasculature is thought not to require VEGF for its survival and function. Thus, the rationale for VEGF inhibition in malignancy is based on the assumption that cancer vessels may be disrupted without harming other parts of the vasculature. There are now a number of antiangiogenic therapies targeting the VEGF pathway, some acting on circulating VEGF (eg, bevacizumab or VEGF trap) and others acting directly on the VEGF receptor (eg, sunitinib, sorafenib, and axitinib). Both approaches are commonly associated with cardiovascular and renal toxicity in the form of hypertension and proteinuria. The mechanisms for these effects, however, remain unclear.

In the present issue of Hypertension, Kappers et al5 present the results of a series of clinical, animal, and in vitro studies aimed at further elucidating the mechanism for the hypertension associated with sunitinib, an orally active multitarget receptor tyrosine kinase inhibitor (RTKI) that inhibits phosphorylation of, among others, the VEGF receptor. They hypothesize that inhibition of the VEGF pathway may reduce NO bioavailability and so promote the development of hypertension. Because the NO system works in balance with the endothelin (ET) system,6 they also investigated the effect of sunitinib treatment on plasma ET-1. Their data are intriguing.

In a small clinical study, 15 patients with metastatic renal cell carcinoma or gastrointestinal stromal tumors eligible for treatment with sunitinib were given the drug for two 4-week blocks with a fixed 2-week washout between. Although there was no placebo comparator, sunitinib treatment led to a significant rise in all of the blood pressure measures, with mean arterial pressure increasing by 10 to 15 mm Hg and returning to baseline once sunitinib was stopped. Interestingly, plasma ET-1 increased alongside blood pressure, although these changes did not correlate, which may well be explained by the fact that 8 of the 15 subjects had to be treated for the hypertension induced by sunitinib. Their studies in rats show a similar pattern with increases in both blood pressure (30 mm Hg) and plasma ET-1 that both return to baseline after sunitinib withdrawal. Based on the single observation that human umbilical vein endothelial cells failed to produce ET-1 in vitro in response to sunitinib, the authors concluded that the increase in ET-1 production is from a nonendothelial source. However, this needs confirming in other endothelial cell types, as does whether the concentration of sunitinib used reflects the clinical situation. It is unfortunate, given their hypothesis, that the authors did not assess NO system activity, although they do show a generalized endothelial dysfunction suggesting, as one may expect, a downregulation of NO activity in response to sunitinib. This may, in turn, lead to an upregulation of ET-1 production (see Figure).

Although suggestive, the findings reported here provide no firm evidence linking a rise in ET-1 as causative in sunitinib-induced hypertension. Indeed, it remains unclear whether this rise is because of an increase in ET-1 production or impairment of its ETB receptor-mediated clearance. This may have been clarified by measuring big ET-1, the precursor peptide in ET-1 synthesis, in the clinical studies and staining for preproET-1 mRNA (eg, in the arteries, heart, and kidneys) in the animal studies. Furthermore, studies using ET receptor antagonists, now widely available, may help address whether ET-1 is an important factor in RTKI-induced hypertension. A recent study in rats showed that the hypertension seen with the multitarget RTKI ABT-869 (known to target the VEGF receptor) could be prevented by pretreatment with the selective ETA receptor antagonist atrasentan.7 Similar studies in humans would be of great interest, because they may potentially support the use of ET receptor antagonists (either selective or mixed) as effective antihypertensive agents alongside VEGF RTKI therapy. Interestingly, ET-1 has been shown to promote angiogenesis in cancer, and so the use of ET receptor antagonists in combination with RTKI therapy in this setting may not only help offset the adverse effects of RTKI but also provide complementary therapeutic antiangiogenic effects.

Another potential mechanism that would link the ET system with RTKI-induced hypertension relates to salt sensitivity. Animal data suggest that treatment with an RTKI selective for the VEGF receptor promotes the development of hypertension that is more marked on a high-salt diet. ET-1...
has an important role in renal tubular salt and water handling, and the rise in plasma ET-1 observed in the current study may be either a cause or consequence of the sunitinib-induced hypertension, which may itself be salt sensitive. The authors provide no data about dietary salt intake in either their clinical or animal studies. Data on sodium balance would be of particular interest if further studies using ET receptor antagonists are pursued. If we are to translate the findings of the animal studies directly to the clinical situation, one may argue that initiation of an RTKI should be accompanied by advice on dietary salt reduction, which would also render any antihypertensive agent more effective.

The renal data presented are of particular interest. In the clinical study sunitinib treatment was associated with a (nonsignificant) rise in urinary protein excretion. This followed the blood pressure pattern, rising with treatment and falling to baseline once treatment was stopped. It is highly likely then that this trend was largely attributable to a transient increase in glomerular perfusion pressure. Although the authors state that there was no change in renal function we must be cautious in their interpretation of the data. Certainly, serum creatinine remained in the normal range. However, significant and irreversible renal damage may occur without impacting on this simple measure of renal function. Indeed, the data presented from the animal studies showed that, whereas proteinuria rose transiently with sunitinib as in the clinical study, creatinine increased ≈3-fold with treatment and remained elevated after treatment withdrawal, suggesting established renal damage. It is unfortunate that the authors do not provide renal histology from their rat studies. There have now been reports of both focal segmental glomerulosclerosis and thrombotic microangiopathy associated with sunitinib treatment in patients with metastatic renal cell carcinoma. In one of these, a thrombotic microangiopathy, which was histologically severe, developed in the face of “normal” renal function, as measured using serum creatinine. These reports, along with the data from the current study, support vigilance in the monitoring of renal parameters such as proteinuria after RTKI initiation and a low threshold for renal biopsy if indicated. Although the renal toxicity with RTKI is more likely to occur alongside hypertension and may well be secondary to this, it is important to note that VEGF probably plays an important role in the adult kidney. Studies in rats show that VEGF maintains glomerular endothelial integrity under physiological circumstances, and VEGF signaling plays a protective role in the kidney in the setting of hypertension. So inhibiting VEGF signaling may clearly lead to renal problems independent of effects on the cardiovascular system. The extent to which ET-1 may be involved in the renal adverse effects of RTKI remains unanswered but should be an avenue of future study.

The studies presented here by Kappers et al represent a laudable preliminary attempt to carry out translational research in a rare condition. Their results provide the platform for future bench and bedside studies that will help further elucidate the mechanisms for the cardiovascular and renal toxicity associated with RTKI, in particular the extent to which the ET system is involved.

Disclosures

None.

References


Receptor Tyrosine Kinase Inhibition, Hypertension, and Proteinuria: Is Endothelin the Smoking Gun?
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