Re: Hypertension as a Biomarker of Efficacy in Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib

Rini et al. (1) reported a large retrospective analysis that showed that patients with metastatic renal cell carcinoma who developed hypertension when treated with the tyrosine kinase inhibitor sunitinib have improved overall survival and progression-free survival compared with patients who remained free of hypertension. The authors concluded that the development of hypertension is a potential valuable biomarker for the prediction of treatment response. However, we wonder whether a categorical division of patients is the most appropriate way to look at the data. Hypertension is defined as a systolic blood pressure of 140 mm Hg or greater and/or a diastolic blood pressure of 90 mm Hg or greater, and this definition was also used in the analysis by Rini et al. (1). However, it is well known that within the so-called normotensive range, a higher blood pressure is associated with an increased cardiovascular risk, indicating that the cutoff values of 140 mm Hg and 90 mm Hg are arbitrary. If a patient has a baseline blood pressure of 138 mm Hg systolic, only a 2 mm Hg increase in blood pressure will classify him or her as being hypertensive, whereas a patient with a baseline systolic blood pressure of 110 mm Hg experiencing a 28 mm Hg increase would not. According to this reasoning, we think that the patient’s absolute or relative blood pressure increase rather than the presence or absence of hypertension is a more appropriate way of analyzing the data. Perhaps, the authors can perform an analysis based on blood pressure increases rather than on the subdivision in hypertension and normotension.

With regard to the mechanism leading to hypertension, the authors mentioned several possibilities. One of these is rarefaction, that is, presence of less-perfused microvessels and/or a diminished number of microvessels. Indeed, rarefaction of skin capillaries during sunitinib treatment in patients with metastatic renal cell carcinoma has been reported (2). In that study, an inverse association between the degree of rarefaction and the increase in blood pressure was observed. This association does not imply causality. The rarefaction could be a consequence of the blood pressure rise. Rarefaction is present in patients with untreated hypertension but is absent when the elevated blood pressure is normalized with an antihypertensive treatment (3). Another point to consider is how much rarefaction is needed to cause blood pressure to increase. A mathematical model based on the hamster cheek pouch microcirculation indicates that 42% rarefaction of the fourth order arterioles is necessary to increase resistance in that particular vascular bed by 5% (4). This estimate suggests that a considerable amount of rarefaction in various vascular beds is required to induce an increase in vascular resistance and hence in blood pressure, assuming that cardiac output remains unchanged. Furthermore, in unrestrained rats in which blood pressure was continuously recorded by telemonitoring, we observed an increase in blood pressure within 1 day of sunitinib administration by oral gavage (5). From this result, it appears that it is highly unlikely that rarefaction is an initial cause of sunitinib-induced hypertension.

One mechanism that was not mentioned by Rini et al. (1) but could potentially underlie the occurrence of hypertension by sunitinib is activation of the endothelin-1 pathway. In the experimental model just described (5) and in patients treated with sunitinib (5), we found that the rise in blood pressure is accompanied by an activation of endothelin-1 pathway. Because renin was suppressed in these patients and we observed no evidence of activation of the sympathetic nervous system or fluid retention, we think that activation of the endothelin-1 pathway is an important mediator of the blood pressure increase induced by sunitinib. This conclusion fits well with the observation that the rise in blood pressure induced by a VEGF receptor tyrosine kinase inhibitor can be largely prevented by endothelin receptor antagonism (6,7). The mechanism by which sunitinib activates the endothelin-1 pathway is still not clear.

References


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