

**chapter 4b – skin microvascular density and blood pressure,
a dynamic relationship**

Sunitinib-induced reduction in skin microvascular density is a reversible phenomenon

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To the editor,

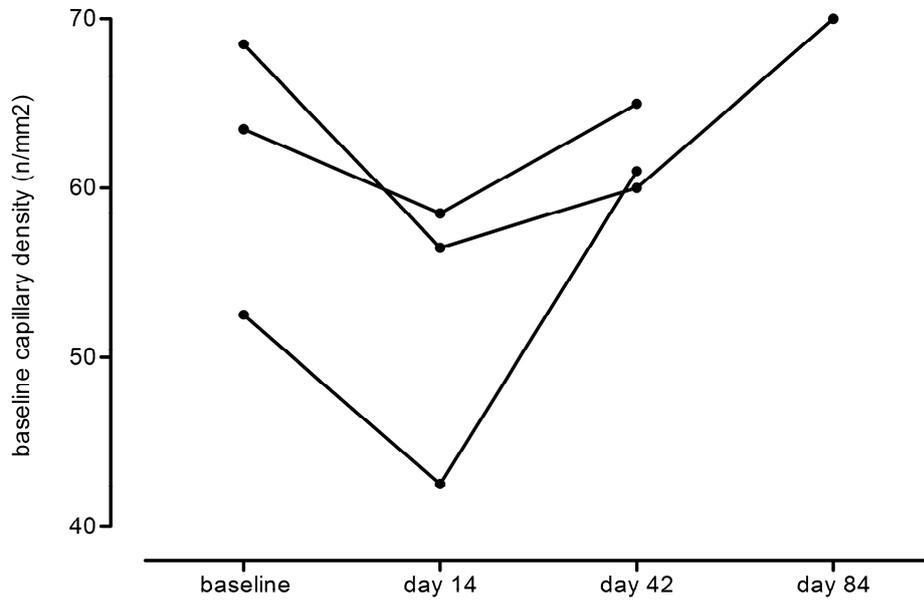
Arterial hypertension is a well recognized adverse event in cancer patients treated with inhibitors that target vascular endothelial growth factor (VEGF) or its receptors (VEGFR). Rarefaction (a decrease in perfused microvessels) is suggested to play an important role in the development of this side-effect (1). A reduction in capillary density has been demonstrated in patients treated with bevacizumab (2), sunitinib (3), and telatinib (4). In the October issue of *Annals of Oncology*, Steeghs et al (5) have demonstrated that the reduction in capillary density induced by bevacizumab was reversible as measured > 3 months upon discontinuation of the drug. Preclinical data in the adult mouse showed rapid reversibility of capillary regression in normal organs within 2 weeks after cessation of VEGF inhibition (6). Whether this is true in humans remains to be demonstrated. We here report rapid and full reversibility of microvessel perfusion upon discontinuation of sunitinib.

The tyrosine kinase inhibitor sunitinib targets VEGFR and is administered in a 4 weeks on 2 weeks off schedule. We have demonstrated earlier that the rise in blood pressure in patients with metastatic renal cell cancer (mRCC) during sunitinib was related with a decrease in capillary density (3). We have also described that the blood pressure rise disappeared promptly during the drug holiday (7). To investigate whether sunitinib-induced reduction in microvascular density is readily reversible within the 2 weeks off treatment, we measured 24-h ambulatory blood pressure and nailfold capillary density (3) at baseline, 14 days after the start of sunitinib 50 mg/day and 14 days after discontinuation of the drug in 3 consecutive patients with mRCC. As reported by us before (3) blood pressure increased, whereas the capillary density decreased. On day 42, 2 weeks after discontinuation of sunitinib, not only blood pressure but also capillary density fully recovered to baseline values in 2 out of 3 patients (figure 1). During the first treatment cycle, the third patient experienced objective sunitinib-induced grade 1-3 toxicities. At the time of cycle 2 she still suffered from a series of grade 1 side-effects which was reason to reduce the sunitinib dose to 37.5 mg/day. Apart from hypertension grade 2, cycle 2 was tolerated well. One week after discontinuation of sunitinib in the 2 weeks off period, antihypertensive medication could be stopped. Measurements of 24-h ambulatory blood pressure and nailfold capillary density were repeated on day 84 (2 weeks after discontinuation of sunitinib at 37.5 mg/day) and promptly showed recovery to baseline values (figure 1). Although the effects of VEGF/VEGFR inhibitors on blood pressure and microcirculation appear to be reversible, it is not known whether prolonged treatment with these drugs will cause permanent damage to the vascular system or even cause structural rarefaction and hypertension as a secondary phenomenon. Currently, these angiogenesis inhibitors are only administered in the palliative setting, but their prolonged administration in the curative setting is under investigation. Therefore, insight is required into potential long-lasting adverse events in normal capillaries that are caused by chronic treatment with these drugs.

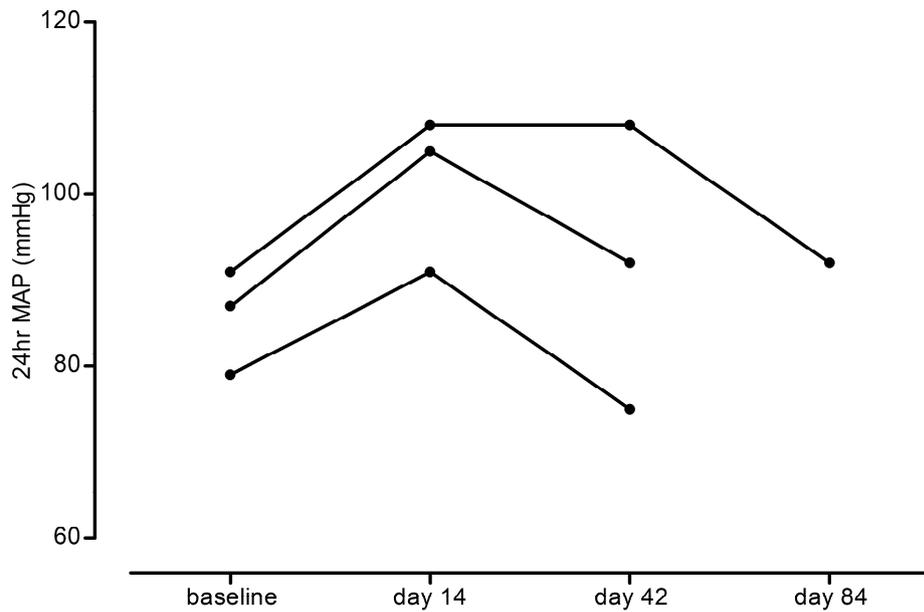
Figures

figure 1

A



B



Measurement of capillary density (A) and blood pressure (B) during the first treatment cycle of sunitinib 50 mg/day in a 4 weeks on 2 weeks off schedule in three individual patients with advanced renal cell cancer. Capillary density is expressed as baseline capillary density in number (n) per square millimeter. In one patient, the sunitinib dose was reduced during the second cycle and additional measurements were carried out after the second off period (= day 84). MAP, mean arterial blood pressure.

References

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