ANGIOGENESIS

Scheduled delivery

One way in which angiogenesis inhibitors, such as bevacizumab (an antibody that neutralizes vascular endothelial growth factor (VEGF)), are thought to improve clinical outcomes in cancer is through the normalization of blood vessels, leading to increased delivery of chemotherapy. Van der Veldt *et al.* report clinical data from patients with non-small-cell lung cancer (NSCLC), which is one of several cancer types that has shown a clinical response to the combination of bevacizumab and cytotoxic chemotherapy, indicating that this hypothesis may not be correct.

The authors conducted non-invasive positron emission tomography (PET) imaging studies in ten patients with advanced NSCLC to monitor tumour perfusion, which indicates vascular status, and the delivery of the chemotherapeutic agent docetaxel following bevacizumab treatment. Perfusion was evaluated using radiolabelled water ($[^{15}O]H_2O$), which is a freely diffusible tracer, at baseline and then at 2 hours, 5 hours and 4 days after a single infusion of bevacizumab. By 5 hours there was a significant reduction in tumour perfusion that persisted until day 4; at day 4, the median percentage change in perfusion of the ten tumours analysed was -38%, with a range of -55% to -4% ($P = 0.005$). To analyse the effects of bevacizumab on chemotherapy delivery, the authors used PET scans following the delivery of a microdose of radiolabelled docetaxel ($[^{11}C]$docetaxel) at baseline and then at 5 hours and 4 days after bevacizumab treatment. The net influx rate constant (K_i) of $[^{11}C]$docetaxel was significantly decreased in tumours at 5 hours and 4 days following bevacizumab administration; the median percentage change in the $[^{11}C]$docetaxel K_i was -34%, with a range of -61% to -16% ($P = 0.005$) at 4 days. Analysis of spatial distributions within tumours showed that similar reductions in perfusion and $[^{11}C]$docetaxel K_i occurred in the centre and the outer edge of tumours, and changes were not correlated with differences in baseline tumour volumes.


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The authors also analysed the systemic effects of bevacizumab. Circulating VEGF levels were significantly reduced following bevacizumab administration. Bevacizumab can also cause cardiovascular side effects, but early changes in blood pressure and cardiac output were not observed, indicating that cardiac effects do not have a role in the decreased delivery of $[^{11}C]$docetaxel to tumours. In addition, $[^{11}C]$docetaxel clearance from the plasma was significantly decreased 4 days after bevacizumab treatment, but this increased systemic exposure did not lead to increased accumulation in tumour tissue.

These data raise interesting questions not only about optimal scheduling of anti-angiogenic drugs, but also about the mechanism by which these agents provide clinical benefit in combination with chemotherapy. The authors propose that vasoconstrictive effects of bevacizumab on tumour vessels may explain the decreased $[^{11}C]$docetaxel delivery, but this hypothesis remains to be tested.

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> “influx … of $[^{11}C]$docetaxel was significantly decreased in tumours at 5 hours and 4 days following bevacizumab administration”

ORIGINAL RESEARCH PAPER Van der Veldt, A. A. M. *et al.* Rapid decrease in delivery of chemotherapy to tumors after anti-VEGF therapy: implications for scheduling of anti-angiogenic drugs. *Cancer Cell* **21**, 82–91 (2012)