Publication

PTK787/ZK222584, a tyrosine kinase inhibitor of vascular endothelial growth factor receptor, reduces uptake of the contrast agent GdDOTA by murine orthotopic B16/BL6 melanoma tumours and inhibits their growth in vivo

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Assessment of tumour vascularity may characterize malignancy as well as predict responsiveness to anti-angiogenic therapy. Non-invasive measurement of tumour perfusion and blood vessel permeability assessed as the transfer constant, K(trans), can be provided by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Using the orthotopic murine tumour model B16/BL6 melanoma, the small contrast agent GdDOTA (DOTAREM(R); Guerbet, Paris) was applied to assess the vascular transfer constant, K(trans), and interstitial leakage space, whereas intravascular iron oxide nanoparticles (Endorem(R); Guerbet, Paris) were used to detect relative tumour blood volume (rTBV), and in one experiment blood flow index (BFI). No correlations were observed between these four parameters (r(2) always <0.05). The B16/BL6 primary tumour and lymph-node cervical (neck) metastases produced high levels of the permeability/growth factor, VEGF. To probe the model, the novel VEGF receptor (VEGF-R) tyrosine kinase inhibitor, PTK787/ZK222584 (PTK/ZK) was tested for anti-tumour efficacy and its effects on DCE-MRI measured parameters of tumour vascularity. Data from the non-invasive measure of tumour vascularity were compared with a histological measurement of vasculature using the DNA-staining dye H33342. PTK/ZK inhibited growth of the primary and, particularly, cervical tumour metastases following chronic treatment for 2 weeks (50 or 100 mg/kg daily) of 1-week-old tumours, or with 1 week of treatment against more established (2-week-old) tumours. After chronic treatment with PTK/ZK, DCE-MRI detected significant decreases in K(trans) and interstitial leakage space, but not rTBV of both primary tumours and cervical metastases. Histological data at this time-point showed a significant decrease in blood vessel density of the cervical metastases but not the primary tumours. However, in the cervical metastases, the mean blood vessel width was increased by 38%, suggesting overall no marked change in blood volume. After acute (2-4 day) treatment, DCE-MRI of the cervical metastases demonstrated

a significant decrease in K(trans) and interstitial leakage space and also in the initial area under the enhancement curve for GdDOTA (IAUC), but no change in the rTBV or BFI. Thus, significant changes could be detected in the DCE-MRI measurement of tumour uptake of a small contrast agent prior to changes in tumour size, which suggests that DCE-MRI could be applied in the clinic as a rapid and sensitive biomarker for the effects of VEGF-R inhibition on tumour blood vessel permeability and thus may provide an early marker for eventual tumour response.
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