Multiple DCEMRI parameters detect necrosis induced by clinically equivalent acute doses of ZD6126 in Hras5 subcutaneous tumours in athymic rat

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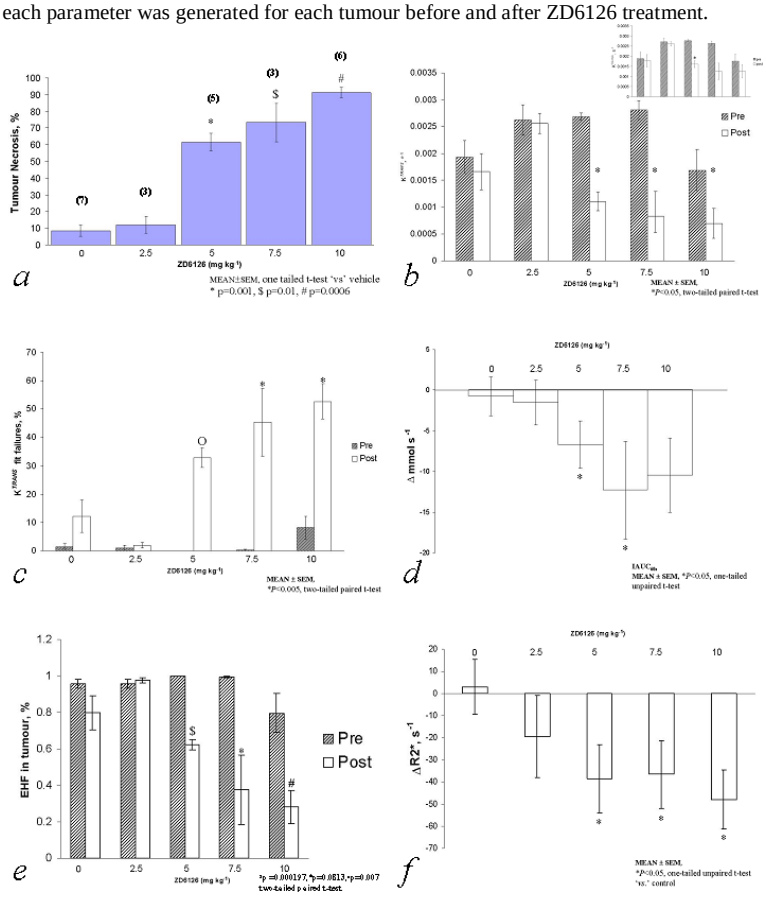
Introduction

The effects of vascular targeting agents (VTA) on tumours in man have been measured using DCEMRI and shown to decrease both K^{TRANS} and initial area under the [Gd]/signal intensity curve (iAUC). Thus, after a single dose of ZD6126, Evelhoch *et al*.,[1] showed an acute decrease in the initial AUC [Gd] with only partial recovery at later times. Similarly, Galbraith *et al*.,[2] demonstrated that a single dose of combretastatin A4 phosphate (CA4P) caused a reduction in iAUC [Gd] curve that showed partial recovery over 24 hours, and that multiple CA4P doses in one patient maintained a reduction in K^{TRANS} from baseline. Galbraith *et al*., suggested that non-enhancing pixels may represent areas of tumour necrosis. Similar DCEMRI findings have also been described in both ZD6126[3] and CA4P[2] treated animal xenograft tumour models. However, Galbraith *et al*.,[2] Evelhoch *et al*.,[3] & Maxwell *et al*.,[4] did not correlate drug-induced changes in tumor DCEMRI measurements with induced tumour necrosis. In contrast, Robinson *et al*.,[5] demonstrated a dose dependent reduction in both enhancing fraction and R_2* associated with correlative scores of tumour necrosis. However, the rat tumour model used in this study had a relatively high background level of tumour necrosis and the ZD6126 doses extended to 50mk/kg, which is likely to give drug exposure levels higher than those expected in the clinic. In addition, it remains uncertain whether VTA-induced changes in DCEMRI measurements are mainly a consequence of one, all or a mixture of changes in tumor blood flow, volume, permeability or necrosis.

Acute (within 6hrs of dosing) changes in tumour vasculature caused by VTAs can be measured by changes in a number of DCEMRI parameters, including iAUC and K^{TRANS} . However, at later times (>6hrs) recovery of tumour vessel function in some areas of the tumour, and induction of widespread necrosis in other areas of the tumour may confound any interpretation of DCEMRI changes. This study was undertaken to investigate whether DCEMRI measurements taken 24hrs after ZD6126 dosing correlated with tumour necrosis, in order to identify potential DCEMRI measures of antitumour activity *in vivo*. Therapeutically relevant doses of ZD6126 (0-10mg/kg i.v.) were administered to athymic rats bearing established Hras5 tumours (ras-transformed mouse 3T3 fibroblasts) and multiple MRI endpoints measured before and 24 hours after treatment. Tumour necrosis was measured and correlated with DCEMRI measurements.

Methods

Male rats bearing Hras5 tumours were established (approx. 1 – 4 cm^3) and then randomly assigned to groups dosed with 0, 2.5, 5, 7.5, or 10mg/kg i.v. ZD6126. Multi-slice T_2W, MGRE and DCEMRI was performed on each animal at 4.7T using quadrature transmit/receive before and 24 hours after a single dose of ZD6126 was administered. After the second imaging time point the tumour was excised for multi-plane H&E analysis and an average necrosis percentage was generated for the whole tumour. Multi-slice K^{TRANS}, iAUC and enhancing fraction (EHF) $_{60/150}$, and R_2* maps were generated form manually drawn ROI's. An average value for each parameter was generated for each tumour before and after ZD6126 treatment.

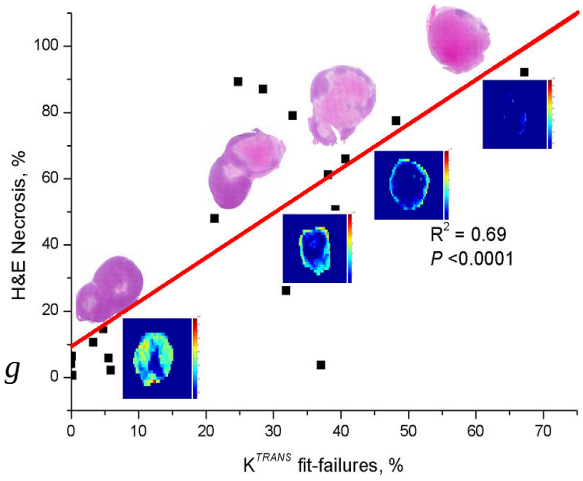


Results

Figures summarise results from tumour either before and 24hrs after and/or changes during ZD6126 treatment (*n* in parentheses). ***a***) Tumour necrosis (H&E) dose response; ***b***) K^{TRANS} including fit-failures that have been set to zero (INSET excl fit-failures, i.e. peripheral sparing as illustrated by parametric maps – See ***g***); ***c***) K^{TRANS} fit failures (O no failures on Day 0); ***d***) change in iAUC; ***e***) the enhancing tumour voxels as a threshold set in normal tissue (longest thoracic muscle); ***f***) change in R2*. R2* may be affected by [dHb], necrosis, haemorrhage and oedema, ***g***) strong and significant correlation between tumour necrosis (%) and K^{TRANS} fit-failures (INSET H&E and K^{TRANS} maps from different dose groups illustrating necrosis and fit-failure, respectively).

Discussion

24 hrs after a single dose, ZD6126 induced significant tumour necrosis and changes in tumour DCEMRI measurements, in a dose-related manner. Multiple parameters were extracted from the DCEMRI measurements along with non-contrast enhanced data, and several correlated strongly with necrosis. Thus, Figure ***g*** illustrates non-enhancing pixels/fit failures correlate with areas of necrosis supporting the suggestion by Galbraith *et al*.,[2] that fit-failures may represent necrotic areas of the tumour. While VTA's may rapidly disrupt tumoural vascular flow, volume and permeability, this current study demonstrates that the therapeutic endpoint of necrosis will greatly influence the final DCEMRI measurement. DCEMRI changes 24 h after ZD6126 treatment correlated with tumour necrosis and may provided a potential measure of the antitumour effects of this agent.



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[1] Evelhoch *et al*., Proc Intl Soc Mag Res Med 2095 (2002), [2]Galbraith *et al*., *J Clin Oncol* **21**, 2831-2842 (2003), [3]Evelhoch *et al*., *Cancer Res.* **10**, 3650-3657 (2004), [4]Maxwell *et al*., *NMR. Biomed* **15**, 89-98 (2002), [5]Robinson *et al*., *Br J Cancer* **88**, 1592-1597 (2003).