Effects of an anti-Angiogenic and anti-Tumour Antibody on Tumour Vasculature determined by Dynamic Contrast Enhanced MRI

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INTRODUCTION Here we present the results of a study using dynamic contrast MRI to measure the vascular properties of an experimental tumour and the effects of treatment. These measures have been shown to be good indicators of the acute effects of treatment with anti-angiogenic cancer drugs. CNTO 95 is a fully human antibody that blocks α_V integrins and inhibits integrin-mediated tumour growth and angiogenesis *in vivo*. It is in Phase I clinical development by Centocor, NJ, USA. In order to determine if CNTO 95 has an effect on the permeability of the tumour vasculature, we used dynamic contrast enhanced MRI in a human melanoma xenograft model in Nude rats.

METHODS MR PROTOCOL: Data were obtained on a 7T (SMIS) scanner. A 2 cm diameter surface coil was used for excitation and detection. A 2D multi-slice gradient echo (GE) sequence was used: TE/TR =5/140 ms; FOV=5cm; flip angle = 90° in the slice-plane through the tumour; 8 contiguous 1 mm slices; 128x64 matrix; 4 averages.
The imaging sequence was run continuously for 90 images (55 min), and Gd-DTPA was injected into the tail vein (0.5 mmol/kg) during acquisition of the 15th image. A region of interest in the slice that received a 90° excitation, encompassing the whole tumour was selected for each image. The average pixel intensity was measured using the imaging software on the scanner.
ANIMAL PROTOCOL: The rat tumour model used was a human melanoma xenograft grown in the flanks of female Nude rats. A375S2 human melanoma cells ($3x10^6$/animal) were injected s.c. Animals were imaged after 2-4 weeks when the tumour reached a diameter of >5mm. All animals were scanned before treatment and then assigned to either a treatment or control group. The treatment group received CNTO 95, injected *i.v.* at a dose of 10 mg/kg, while the control group was injected with an equivalent volume of saline. Each animal was scanned three times: pre-treatment, and on days 1 and 3 after treatment. Animals were anaesthetized with halothane/O_2 during scanning.

RESULTS The signal intensity from the images resulting were analysed with a compartmental model (1) which allows an estimation of the initial rate of enhancement as a measure of vascular permeability, VP and exchange rate, k_{ep}.

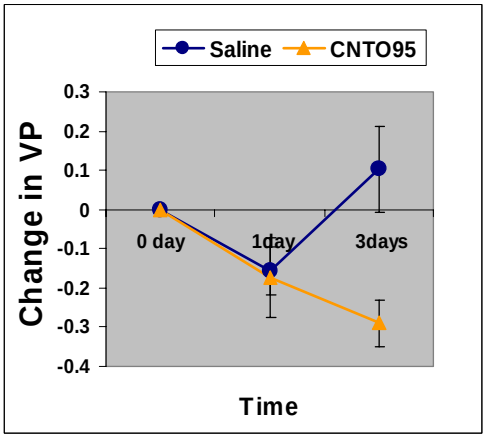

Fig.1

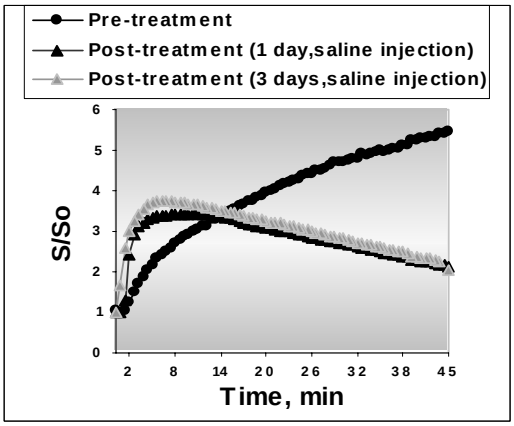

Fig.2

Fig.1 shows the results of analysis of the data for two groups of animals (saline and CNTO treatment) with 3 rats in each group. Change in VP is the difference in post-treatment and pre-treatment means of VP. There is a significant difference ($p=0.036$, repeated measures, general linear model in SPSS between groups (saline and CNTO 95)) in the change of VP at 3 days after treatment. The two groups show opposite behaviour. VP decreases at 3 days after CNTO 95 injection for each animal, while saline-treated tumours show some increase in VP after 3 days. There were no significant effects of time or treatment on the exchange rate. Analysis of the data indicated some differences between tumours. Some tumours enhanced less rapidly than the others. Marked differences in the time taken for the Gd-DTPA uptake to reach saturation were found both between animals and during repeat scanning of one animal (Fig.2). Two types of saturation could be an indicator of the different stages of angiogenesis. For the purposes of this analysis we only considered data from tumours which exhibited fast enhancement at all time points (e.g. data from animals such as the one shown in Fig.2. were excluded).

CONCLUSIONS A significant difference in the change of VP between groups (saline and CNTO 95) after treatment confirms the anti-vascular effects of the therapeutic action. The increase in VP in 3 days for some control animals is probably connected with further tumour growth and a corresponding progression of angiogenesis. There is a difference in saturation time that could be an indicator of the different stages of angiogenesis.

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REFERENCES 1. P.S. Tofts, A.G. Kermode, *Magnetic Resonance in Medicine*, **17**:*357-367 (1991).*