Differential effects of VEGF-trap on benign and malignant human melanoma xenografts evaluated by DCE MRI

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Introduction

K^{trans}, the first order rate constant, that describes the transfer of contrast agent molecules from the vasculature to the interstitium, is a non-invasive indicator of changes in perfusion and/or permeability of tumor capillaries induced by antiangiogenic drugs. Based on our previous development of a DCE MRI protocol which permits simultaneous measurement in mice the arterial input function (AIF) of gadodiamide and its uptake into the tumor [1], here we evaluate the effect of an antibody to the vascular endothelia growth factor (VEGF), namely VEGF-Trap, on a highly metastatic and a non-metastatic melanoma xenografted in mice.

Materials and Methods

Animal Preparation: Highly metastatic (C8161) or non-metastatic (A375P) human melanoma cells were inoculated subcutaneously into nude mice (10^6 cells in 50 µl). For each tumor type, mice were divided randomly into two groups (n=19 in each group) to receive either VEGF-Trap or the control IgG protein (both provided by Regeneron Pharmaceuticals, Tarrytown, NY), assigned as A- or B-tube and unknown to the researchers until the end of the study. The drug was given at 25 mg of protein /kg s.c. twice a week for 3 weeks starting at 3 weeks after tumor inoculation.

MR Imaging: All MR experiments were performed with a Unity INOVA console (Varian, Palo Alto, CA) interfaced to a 4.7 T horizontal bore magnet and a 12 cm gradient insert capable of generating magnetic field gradients of up to 25 G/cm. A home-built 4.5x 9 cm linearly polarized birdcage RF coil was used for A375P study and a combination of TEM transmit volume coil and surface receive coil (InsightMRI, Worcester, MA) was used for C8161 study. Single-slice acquisition was conducted in A375P study while multi-slice acquisition with at least one slice covering the left ventricle was performed in C8161 study. All MR acquisitions were ECG gated. T2W images were acquired to delineate tumor boundary and T10 (precontrast T1) map was acquired as described previously [2]. Sixty images were acquired using saturation-recovery GRE sequence (TE/TR =2.2/6.0 ms, FA= 90°, matrix of 128 x 16 and single average) followed by a second series of 120 images using identical parameters but two signal averages. Gadodiamide (Omniscan, Princeton, NJ) at 0.1 mmol Gd/kg was injected in a bolus (in 0.1ml) after acquisition of 20 pre-contrast images. There are 3-5 mice per group enrolled in MR experiements.

Image Processing: Tumor boundary was defined on T2W images and then applied on DCE images. Tumor was segmented into peripheral and central region on DCE images: pixels less than 1.88 mm (or 4 pixels) inward from the boundary were defined as tumor periphery and those at least 3.28mm (or 7 pixels) inward from the boundary are considered as tumor center. AIF and the time course of the R1 relaxation rate constant of the tumor were extracted from intensities of DCE images, and were fitted into the *BOL*us *E*nhanced *R*elaxation *O*verview (BOLERO) model [3] to derive K^{trans}.

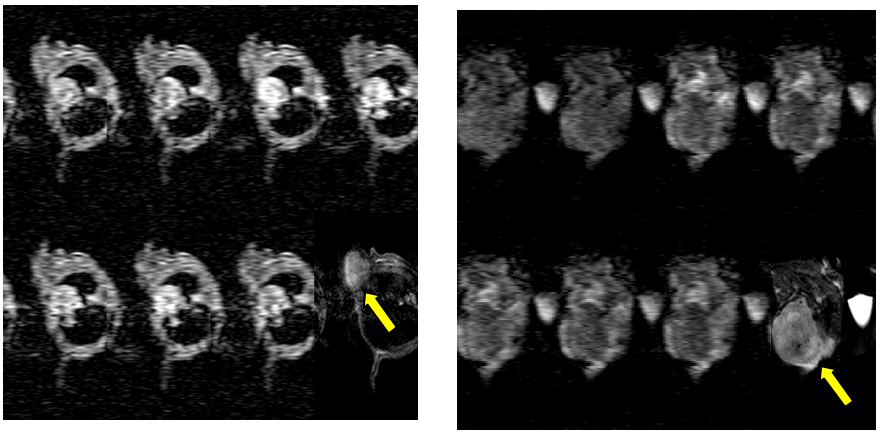


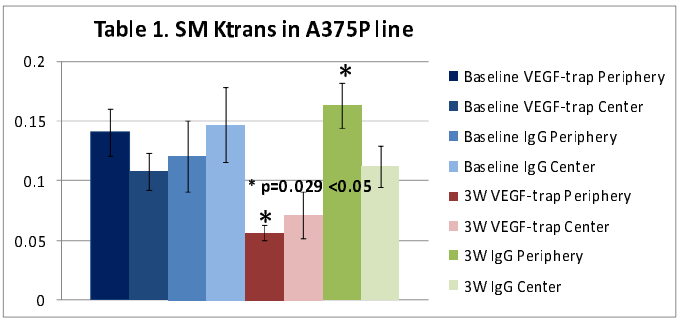
Figure1 shows selected DCE images from a A375P (left) and C8161 (right) xenograft treated by VEGF-trap. Tumors are noted by arrows on T2W images. After the bolus (starting from 3rd image), the A375P tumor has uniform signal increase within the tumor, while the C8161 tumor's periphery has noticeable signal increase but the central part remains unenhanced.

Results and Discussion

For both A375P and C8161 tumors, the tumor volume of VEGF-trap treated group was significantly smaller than IgG treated group. DCE MRI results suggest K^{trans} was significantly reduced in the periphery of A375P treated by VEGF-trap compared to IgG (p=0.029). While Ktans in the periphery of C8161 tumor was smaller in VEGF-trap treated group than in IgG treated group, it failed to reach a statistical significance from the data we have analyzed so far. Preliminary histological data suggests that C8161 tumor expresses high level of CD31 (endothelial marker), which is mismatched by perfused capillaries visualized by fluorescent dye perfusion. Therefore, it is possible that VEGF-trap treatment eliminate the nacent (non-perfused) vessels while not having profound effect on functional ones. Other studies are being performed to explain the lack of K^{trans} response in metastatic tumors treated by VEGF.

References:

(1) *Magn Reson Med. 2004 52(2):248-57.*
(2) *Magn Reson Imag 1990,8:351–356.*
(3) *Magn Reson Med 2003;50:1151–1169.*



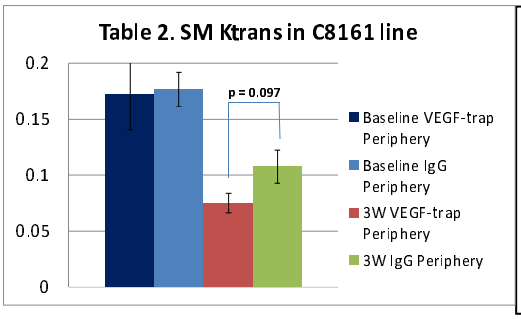


Table1 and 2 shows the mean K^{trans} values within segmented tumor periphery and centre under the noted categories. SM K^{trans} is evaluated under the fast-exchange-limited (FXL) assumption.