Magnetic resonance imaging demonstrating reduction of edema by anti-angiogenic treatment in a brain metastasis mouse model

L. Zhang, J. Munasinghe, J. Yin, A. Koretsky, and K. Kelly

Background
Brain metastases occur in 10-30% of cancer patients with solid extracranial tumors. These tumors are commonly angiogenic and disruption of the blood brain barrier results in edema through the accumulation of extracellular fluid. This vasogenic edema causes injury through raising the intracranial pressure and displacement and damage of brain tissue, resulting in morbidity and mortality. Current treatments of both the brain metastasis and ensuing edema are limited and cause undesirable side effects. We have previously described a xenograft mouse model of brain metastasis which produces angiogenic tumors. AZD2171, a VEGF receptor antagonist, has been shown to relieve edema in glioblastoma patients. We are currently using this model to study the effects of AZD2171 on edema using MRI T2 scans and diffusion weighted imaging (DWI).

Methods
Male athymic nude mice were injected in the left cardiac ventricle with DU145/RasB1, a ras-transformed human prostate cancer cell line. The cells contain a luciferase reporter gene which allows for monitoring of brain metastasis growth. At 4 weeks, six mice showing positive brain signal in bioluminescence imaging (BLI) had T2 and DWI scans performed on a 7-T horizontal scanner. T2 values were obtained with a CPMG multi-echo sequence with TR=3000ms and echo spacing of 15ms. DW images were obtained in three axes (2 b values of 0.7 and 1500 second/mm², TE / TR = 23.5 / 3000 ms) and Apparent Diffusion Coefficient (ADC) values calculated. The six mice were then divided into treated and untreated groups. After 1 week, we acquired a second set of T2 and DW images. Brains were then collected and fixed for staining with luxol fast blue to confirm the presence of edema.

Results
Sequential T2 scans revealed rapid development of edema in an untreated mouse (Figure 1). The edema is seen following the white matter tracts, causing high T2 and ADC values in brain regions such as the hippocampus. T2 scans also showed extensive edema and its subsequent reduction after treatment (Figure 2). DWI had similar results. Luxol fast blue staining of untreated mice showed areas of enlarged extracellular space by tumors (Figure 3). This confirms the presence of edema in mice which demonstrate edema by MRI T2 scans and DWI.

Discussion
We have established a mouse model that develops brain metastasis associated vasogenic edema, an important factor in morbidity and mortality in humans. This model is useful in evaluating therapeutic agents for brain metastasis. Non-invasive MR imaging has allowed us to monitor the effect of a VEGF receptor inhibitor on edema over time. Mice developed edema rapidly without treatment, while edema was reduced in mice receiving treatment. This coincides with our previous blood volume data, which showed an increase of blood vasculature without treatment, and a decrease of blood vasculature with treatment. Edema reduction is likely from reduced leakage of the blood vessels due to angiogenesis inhibition, allowing the accumulated fluid to drain naturally from the brain. Anti-angiogenic agents, most likely in combination with other therapeutics, are being actively investigated for the treatment of primary and metastatic brain tumors. The use of non-invasive imaging similar to that shown here is anticipated to be an important tool in evaluating parameters of the functional response to anti-angiogenic agents.