Diffusion-Weighted MRI As An Early Predictor of Response To Sunitinib

R. M. Stephen[1], D. Zhao[2], and R. J. Gillies[2]

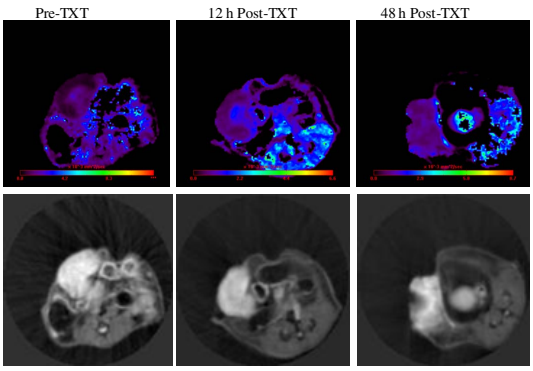
[1]Cancer Center, University of Arizona, Tucson, AZ, United States, [2]University of Arizona

Introduction Breast cancer is the second leading cause of death in American women [1]. Vascular endothelial growth factor (VEGF) is a potent angiogenic factor involved in tumor progression. Increased levels of VEGF expression have been associated not only with decreased response to therapy (hormonal and chemotherapy) but also with relapse-free and overall survival in both node positive and node-negative breast carcinomas[2]. VEGF upon binding to VEGF receptor(VEGFR) initiates the start of the tyrosine kinase signaling cascade that stimulates the production of proangiogenic factors that promote vessel permeability (eNOS, producting NO), proliferation/survival (bFGF), migration (ICAMs/VCAMs/MMPs) and finally differentiation into mature blood vessels. Antiangiogenic agents inhibit tumor growth by preventing new blood vessel formation. Current anti-angiogenic therapies are targeted against either VEGF or its tyrosine kinase receptors. Sunitinib, a small molecule tyrosine kinase inhibitor, is a potent inhibitor of VEGFR1 and 2, PDGFRα andβ, and c-KIT[3]. The purpose of this study was to examine the role of DW-MRI and DCE-MRI in predicting the early response of sunitinib in breast tumor xenografts prior to changes in tumor volume.

Methods In this study, MD-MBA-231/GFP cells were grown as orthotopic xenografts in 4-6-week old female SCID mice (n=8). When tumor volumes reached 400 mm^3, pretherapy images were acquired. Approximately 48 h later, the animals were treated with either 40 mg/kg of sunitinib or a carboxymethylose carrier qd for 14 days. The animals were imaged again within 12 h of the first dose and 48 h following the last dose. DW-MRI images were acquired on a 4.7 T Bruker Biospec using the following parameters: TR = 2000 ms, TE = 40 ms, matrix size = 128 mm x 128 mm, FOV = 3.0 mm x 3.0 mm. At each slice location, images were obtained at three b values (25, 500, 950 sec/mm^2) [$b = \gamma^2 G_d^2 \partial^2 (\Delta - \partial/3)$, where G_d is the strength of the diffusion weighting gradient and γ is the gyromagnetic ratio for protons (42.58 MHz/T) and ∂ and Δ represent duration and separation of diffusion gradients, respectively] over 20 min. Regions of Interest (ROI) were drawn around the tumor and ADC maps were generated.

Results and Discussion An increase in ADC values was observed in tumor xenografts as early as 12 h (n=4; ADC = 826 mm^2/sec) following the first dose and continued until 48 h posttherapy (ADC =1052 mm^2/sec) compared to pretherapy values (n=4; ADC =785.5 mm^2/sec; Figure 1). The changes in diffusion at 12 h are the earliest time that changes have been observed in ADC in response to a chemotherapy to date. Based on our results, DW-MRI was able to predict the early response to sunitinib prior to changes in tumor volume. Additionally, our preliminary findings identified tumor vascular changes following treatment with sunitinib using DCE-MRI. DCE-MRI with both low and high molecular weight contrast agents (Gd-DTPA and Gd-DTPA-BSA, respectively) showed decreased permeability in response to sunitinib (data not shown). DW-MRI and DCE-MRI may be a useful pre-therapy test in identifying patients that will be responsive to anti-angiogenic therapies.

Figure 1.



References

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