

EARLY RESPONSES OF BREAST CANCER PATIENTS TO CHEMOTHERAPY WITH AND WITHOUT ANTI-ANGIOGENIC PRE-TREATMENT MONITORED BY DIFFUSION TENSOR IMAGING

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Target Audience: Scientists and clinicians who are interested in using the advanced DTI and DCE-MRI techniques for understanding the pharmacokinetics and vessel normalization effect of anti-angiogenic agents used in conjunction with chemotherapy in breast cancer treatment.

Purpose: Diffusion weighted MRI can be used to probe water diffusion and hence the tissue microstructure in vivo. It has also been used to assess the early response of tumor tissue vasculature to anti-angiogenesis agents, chemotherapy and radiotherapy. In this study, we hypothesize that intermittent administration of low dose anti-angiogenesis agent, Sunitinib, to breast carcinoma patients prior to conventional chemotherapy may normalize tumor vasculature and increase the delivery of anti-cancer molecules to tumor cells and hence improve the chemotherapy effectiveness. Here, we report our findings in serial diffusivity changes in response to different treatment regimens of advanced breast cancer as obtained from Diffusion Tensor Imaging (DTI) noninvasively.

Methods: Thirty-five advanced breast cancer patients were recruited for this IRB approved clinical trial. Signed IRB consent forms were obtained from all patients. Patients were 1:1 divided randomly into Arm A and B. Arm A (n=18) received only chemotherapy that consisted of Doxorubicin (60 mg/m²) and Cyclophosphamide (600 mg/m²) (AC) for 14 days (1 cycle). Arm B (n=17) patients pre-treated orally with Sunitinib (Su) at 12.5 mg daily for 7 days, then proceeded to receive the same chemotherapy as in Arm A. All patients underwent DTI prior to treatment (pre-Tx) and after one cycle of chemotherapy (post-AC or post-(Su+AC)), while Arm B patients had one additional scan after Su treatment (post-Su) for investigating the effect of low dose Sunitinib. All MRI scans were performed with a 3T whole-body scanner (Magnetom Trio Tim, Siemens AG, Germany) using a seven-channel breast receiver coil. DTI acquisition incorporated a sagittal diffusion-weighted EPI sequence: TR/TE = 7500/116 ms, NEX = 3, flip angle = 90°, matrix size = 96×96, FOV = 180×180 mm, slice thickness = 3.0 mm. Diffusion gradients were applied in six directions with $b = 0$ and 600 s/mm². Both ADC and fractional anisotropy (FA) values were analyzed. Dynamic contrast-enhanced (DCE) MRI was also performed¹ (interpolated matrix size = 256×256, FOV = 320×320 mm, slice thickness 4.0 mm, slice number = 16, slice gap = 0), and tumor ROIs were drawn slice by slice using these acquired images. These ROIs were transformed onto DTI images for measuring the tumor ADC and FA values. Tumor volumes before treatment (pre-Tx) (V_1) and post-treatment (post-AC or post-(Su+AC)) (V_2) were calculated. Relative change in tumor volumes were calculated as $(V_2 - V_1)/V_1$.

Results and Discussion: Fig. 1 is an illustration of ADC map from a patient with advanced breast carcinoma studied. Quantitative tumor volumes measured by 3D DCE-MRI images showed reduction from $34.6 \pm 7.2 \text{ cm}^3$ to $23.4 \pm 6.1 \text{ cm}^3$ ($p = 1.92E-03$) in Arm B while showed less reduction from $44.5 \pm 13.0 \text{ cm}^3$ to $39.0 \pm 13.3 \text{ cm}^3$ ($p = 8.82E-03$) in Arm A (Fig. 2). Compared to pre-Tx, ADC values significantly increased in patients received Sunitinib pretreatment plus one cycle of chemotherapy (Arm B, $p = 2.00E-04$) (Fig. 3a) and also in those solely had one cycle of chemotherapy (Arm A, $p = 7.94E-04$) (Fig. 3a).

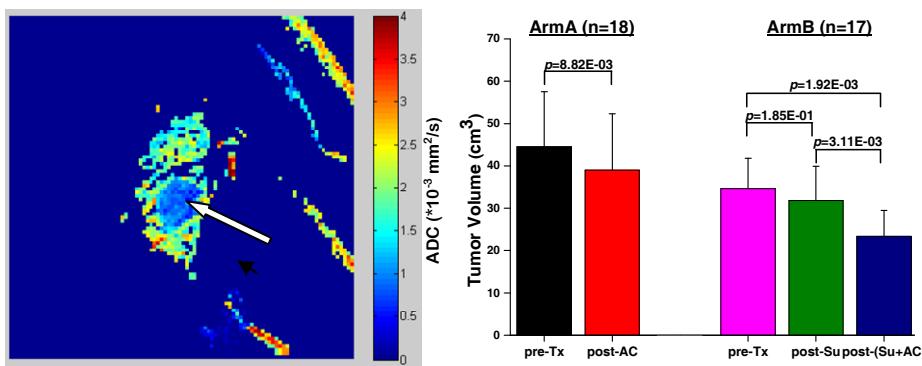


Fig. 1 An example of sagittal ADC map from an advanced breast carcinoma (pointed by arrow). **Fig. 2** Tumor volume changes (mean \pm SE) measured at different stages of treatments.

tumors with lower pre-treatment ADC values are likely going to respond better to chemotherapy. Similar patients who underwent radiotherapy³. Our results show that the measured whole tumor ADC values could be a biomarker and might even be a predictor for breast cancer in response to chemotherapy.

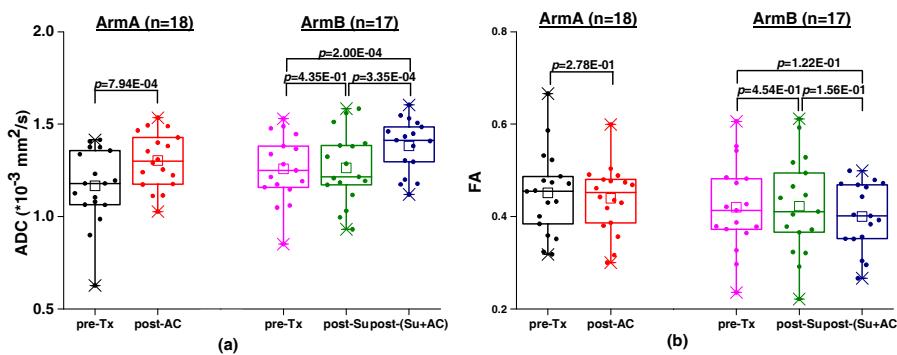


Fig. 3 Box plots of ADC values (a) and FA values (b) in all patients before treatment (pre-Tx in Arm A and Arm B) and after treatment (post-AC in Arm A, post-Su and post-(Su+AC) in Arm B).

However, the results indicate that patients pretreated with Sunitinib resulted in increased ADC more significantly (with lower p values) than those who didn't. The results imply that anti-angiogenesis Sunitinib may have enhanced the chemotherapy effectiveness, probably by normalizing the vasculature² and thus increase the outcome after the first chemotherapy cycle. The 7-day Su treatment itself did not result in significant changes in ADC values (post-Su, Fig. 3a), probably due to low dose. All treatments did not exhibit any significant changes in FA values at the time points studied (Fig. 3b). Pre-treatment ADC values and the relative changes in tumor volumes after treatments were correlated for both Arm A ($r = 0.75, p = 3.14E-04$) and Arm B ($r = 0.57, p = 1.79E-02$) (figures not shown). The correlation results suggest that breast

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