Evaluation of metronomic chemotherapy in a mouse model using DCE-MRI and DWI

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TARGET AUDIENCE: Researchers interested in evaluation of cancer therapy response

PURPOSE: Metronomic chemotherapy (MCT) has been proposed as a method for improving tumor response while minimizing the severe side effects that are common with traditional chemotherapy. MCT is administered in relatively low doses in a near continuous manner as opposed to traditional chemotherapy, which is administered in high doses at relatively sparse intervals[1]. Although studies using MCT have shown promising results that suggest it may be superior to traditional chemotherapy[2,3], there is a need for additional studies to optimize MCT dose and scheduling for individual cancer types. The purpose of this study was to investigate the use of 4T1 mouse mammary tumor cells implanted in BALB/c mice as a locally advanced breast cancer model for MCT dose optimization using dynamic contrast enhanced (DCE) MRI and diffusion weighted imaging (DWI).

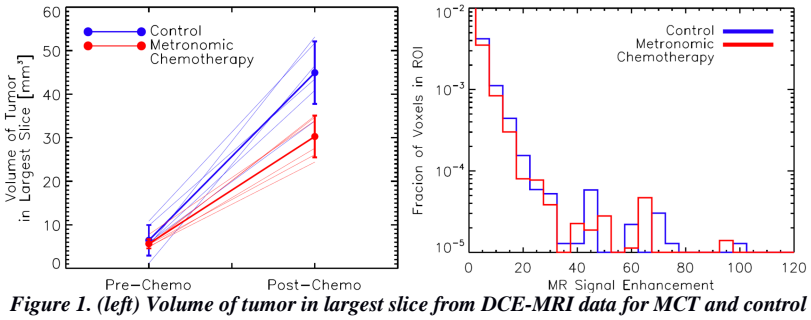

Figure 1. (left) Volume of tumor in largest slice from DCE-MRI data for MCT and control groups before and after receiving chemotherapy. (right) Histogram of MR signal enhancement from DCE-MRI data for MCT and control groups.

METHODS: Six- to eight-week-old BALB/c mice (n=12) were injected in the mammary fat pad with 10^5 4T1 mouse mammary tumor cells suspended in 0.1 ml of PBS on day 0. All of the mice were scanned on day 7 and day 17. On days 7, 9, 11, 14, and 16 the mice were given an intraperitoneal injection of either 40 mg/kg of 5-Fluorouracil in saline for the metronomic chemotherapy (MCT) group (n=6) or an equivalent volume of saline (n=6) for the control group. MRI was performed using a 7T horizontal bore magnet with a volume transmit and receive coil. General anesthesia was induced by 1.5% isoflurane in air. The animal was mounted on a cradle with respiratory and temperature monitoring probes. A T2-weighted rapid acquisition with relaxation enhancement (RARE) sequence was used (TR = 2s, TE = 35ms, FA=180º, res = 0.125 x 0.125 x 1.5 mm) to select 8 slices near the tumor center. T1-weighted 3D FLASH data (resolution=0.1 x 0.1 x 1.0 mm^3, FA=8 degrees, TE=3.5 ms, TR=12.5 ms, 70 repetitions, 13.6 s/rep) were acquired and 0.1 ml/kg Gd-DTPA was injected intraveneously 3 minutes after the start of data acquisition. Regions of interest were drawn by hand for several slices that included the lesion. The volume in the slice with the largest ROI was calculated and a histogram of MR signal enhancement was generated for all voxels in the ROI. A pulsed gradient spin echo (PGSE) diffusion measurement (δ = 7ms, Δ = 14 ms) was performed with 16-shot echo planar imaging sequence (TR = 3.0 s, TE = 32 ms, resolution = 0.23 x 0.4 x 1.5 mm). The diffusion weighting gradient was varied from 0 to 28 G/cm to have diffusion weighting of b = 5, 39, 68, 96, 123, 177, 231, 337, 442, 546, 650, 753, and 857 s/mm^2. The apparent diffusion coefficient (ADC) was estimated by fitting a monoexponential model to the data. This study was approved by the institutional animal care and use committee.

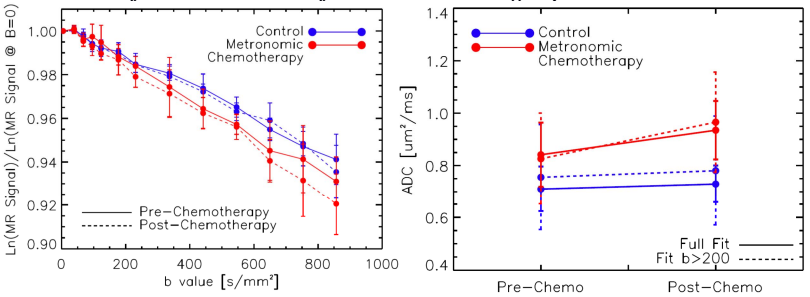

Figure 2. (left) Log of normalized MR signal from DWI data versus b value for MCT and control groups before and after receiving chemotherapy. (right) Estimated ADC values for MCT and control groups before and after receiving chemotherapy. Estimates were calculated using all b values and only b values greater than 200 μm^2/ms.

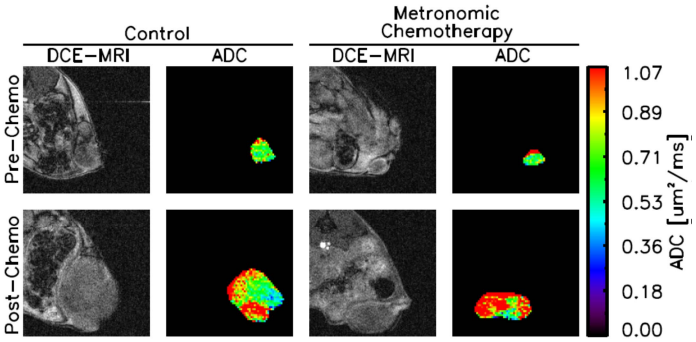

Figure 3. Post-contrast DCE-MRI images and ADC maps of example lesions for the MCT and control groups before and after receiving chemotherapy.

RESULTS: Tumor volumes for the MCT group were significantly lower than for the control group ($p<0.01$) on day 17 after receiving treatment. Post-contrast DCE data showed no difference in fraction of enhancing voxels between the MCT and control groups. There was no significant difference between ADC values estimated from fits to data for all b values and fits to only data for only b > 200, suggesting a lack of intra-voxel incoherent motion (IVIM) effect in the tumors. For ADC values estimated using all b values, there was no significant difference between MCT and controls groups for pre-chemotherapy measurements, however, there was a significant difference between these groups for post-chemotherapy measurements ($p<0.01$). When estimating ADC using only b > 200 values, there was no significant difference between MCT and control groups for post-chemotherapy measurements.

DISCUSSION: Tumor volume data indicate that metronomic chemotherapy treatment with 5FU of mice implanted with 4T1 mammary tumor cells reduces the tumor volume 10 days after the initiation of therapy. Despite the reduced tumor volume, no change could be detected in the contrast enhancement of these tumors that typically have poor and limited enhancement in the rim. DWI data suggested a lack of perfusion that can be detected by IVIM measurement in the tumors as well. ADC estimates were sensitive to treatment changes when all of the acquired data was used.

CONCLUSION: Mice implanted with 4T1 cells may provide a good model of advanced breast cancer since they develop tumors that are poorly perfused. DWI appears to be sensitive to early response to treatment. Future study is warranted to investigate the feasibility of improving the perfusion and drug delivery in this challenging tumor model.

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REFERENCES: 1. Jain (2005; Science, 307, 58) 2. Browder et al. (2000;Cancer Res, 60, 1878) 3. Man et al. (2002; Cancer Res, 62, 2731).