Combining DCE-MRI and DW-MRI for evaluating the early response of a hypoxia-activated chemotherapy

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Abstract: We have used DCE-MRI and DW-MRI to investigate the biological response to TH-302, a hypoxia-activated bis-alkylating prodrug in a pre-clinical model of pancreatic cancer. As a consequence of TH-302 selective effects on poorly-vascularized tumor regions, we expected a change in DCE-MRI and/or DW-MRI. The results showed that TH-302 caused a change in tumor vasculature as measured with DCE-MRI, but did not change cell membrane integrity measured with DW-MRI. These effects were homogenous throughout the tumor. These results demonstrate advantages of combining DCE-MRI and DW-MRI for therapy studies.

Introduction: TH-302 is an investigational agent that is currently in Phase II clinical trials for treatment of pancreatic cancer. TH-302 is an inert prodrug that is activated in hypoxic tissues.[1,2] Although the effects of TH-302 have been studied in vitro and in vivo, pre-clinical imaging studies may further elucidate the timing and spatial tissue distribution of the biological effect.[3] Specifically, we sought to determine if the initial response affected tumor vasculature or tumor cell viability, the duration of this response as measured with MRI, and the spatial distribution of the therapeutic effect within the tumor. We conducted Dynamic Contrast Enhancement MRI (DCE-MRI) and Diffusion Weighted MRI (DW-MRI) to investigate TH-302-induced changes in tumor vascular permeability and cell membrane integrity, respectively.

Methods: Pre-clinical studies were conducted with the approval of the IACUC at our institution. A subcutaneous tumor model of MiaPaCa2 pancreatic cancer was prepared with female SCID mice aged 6-8 weeks old. Tumors were allowed to grow for 21-23 days to an average size of 250 mm^3 before initiating MR imaging and treatment. Seven mice were treated with TH-302 and 6 mice were treated with vehicle as a control. A volume of 125 µL of 10 mg/mL TH-302 in saline was injected i.p. (50 mg/kg for a 25g mouse) on Day 0-3 and 6-10 relative to starting therapy on Day 0. MRI was performed on Days -1, 1, and 10.

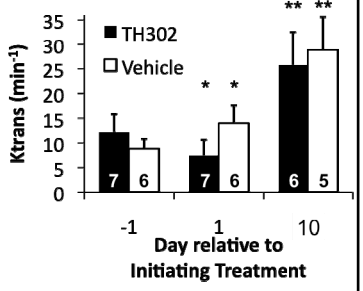

Figure 1. The average Ktrans significantly decreased 1 day after TH-302 treatment while Ktrans significantly increased relative to Day -1 with vehicle treatment. Average Ktrans of both treatment groups significantly increased by Day 8 relative to Day -1 (* represents $p<0.05$, ** represents $p<0.01$). Average Ktrans was significantly different between treatment groups on Day 1 ($p<0.05$) but not on Day -1 or Day 8. The number of mice scanned per time point is listed on each bar.

DCE-MRI studies were conducted by acquiring image slices through the xenograft flank tumor, the renal artery and the femoral artery.[4] The following MRI parameters were used: 250 msec TR; 8.2 msec TE; 0.5 mm slice thickness; 273x273 um in-plane resolution; 3.5x3.5 cm field of view; 2 averages. A total of 60 image sets were acquired for a total acquisition time of 32.0 min and a temporal resolution of 32 sec/image. After the fifth image set was acquired, 0.2 mmol/kg Gd-DTPA was injected i.v. in a total volume of 0.25 mL during 60 seconds. DCE-MRI results were analyzed using the Patlak method to obtain parametric maps of Ktrans and fractional plasma volumes.[5]

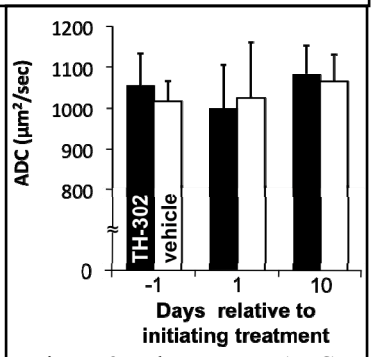

Figure 2. The average ADC did not significantly change between days or groups.

DW-MRI studies were conducted using a diffusion-weighted radial echo pulse sequence and the following MRI parameters: 1000 msec TR; 40 msec TE; 1.5 mm slice thickness; 400x253 µm in-plane resolution; 5.12x5.12 cm field of view; 1 average; 20:12 total acquisition time; 25, 400, and 750 s/mm^2 b-values.[6] Cross terms between diffusion-weighting gradients and imaging gradients were taken into account when determining b-values, and the phase of the MRI gradients were iterated along three axes to account for tissue anisotropy. Results were processed to create parametric maps of the ADC.

Results: DCE-MRI produced more precise results with an Arterial Input Function derived from the femoral artery than the renal artery. Careful control of other physiological and experimental conditions also contributed to the excellent precision of Ktrans measurements.[4] DCE-MRI results showed a significant decrease in Ktrans after one day of TH-302 therapy, which was significantly different than the increase in Ktrans in the control group (Figure 1). This decrease was homogenously distributed throughout the tumor. With this treatment regimen, Ktrans was significantly higher in both treated and vehicle groups at Day 10. Vascular plasma volume measurements form DCE-MRI and ADC measurements from DW-MRI results did not change after TH-302 treatment or vehicle treatment (Figure 2).

Discussion: This study indicated that TH-302 had a significant early change on tumor vascular permeability, but a measurable effect on cell membrane integrity or vascular volume was not observed. This study demonstrates the advantages of performing DCE-MRI and DW-MRI within the same pre-clinical study.

References:

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