Comprehensive Magnetic Resonance Monitoring of Tumoricidal Effect of a Vascular Targeting Agent in a Rodent Liver Metastatic Model

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PURPOSE: To noninvasively monitor post-therapeutic events after intravenous injection of a vascular targeting agent (VTA) in rats with liver tumors by using comprehensive magnetic resonance (MR) techniques in correlation with microangiographic and histological findings.

METHODS: Thirty rhabdomyosarcomas (R1) of 8-12 mm in size were available two weeks after implantation in the liver of 15 rats to mimic liver metastasis. Using a 1.5 T clinical MR scanner and a 4-channel wrist coil, T2-weighted (T2WI), pre- and post-contrast T1-weighted (T1WI), diffusion-weighted (DWI), and dynamic susceptibility contrast-enhanced perfusion-weighted (DSC-PWI) MRI with regional blood volume (rBV) and flow (rBF) maps were acquired at baseline, 1h, 6h and 2 days after intravenous injection of the VAT Combretastatin A-4-phosphate (CA4-P, n = 9) at a dose of 10 mg/kg in comparison with saline-controls (n = 6). In vivo data including tumor volumes, signal intensity (SI), apparent diffusion coefficient (ADC), rBV and rBF were correlated with ex vivo microangiography and histopathology. Proton MR spectroscopy (1H-MRS) was also attempted in 15 R1 tumors.

RESULTS: Being clearly depicted on plain T2WI and T1WI, the tumors grew significantly slower in VTA treated than that in control rats ($p<0.01$). On post-contrast T1WI, dramatic vascular shutdown of R1 tumors occurred in VTA treated rats as early as 1 h and became more prominent at 6 h (Fig. 1). Tumor relapse with peripheral angiogenesis appeared as rim enhancement 2 days after treatment. Functional changes on tumoral perfusion and diffusion could be documented with PWI and DWI. Both ADC map and high b-value DWI enabled discrimination between necrotic and viable intratumoral components ($P<0.01$). In comparison with the controls, tumoral rBV and rBF sharply decreased 5 and 8 times during 1 to 6 h, and partly recovered at day 2 in VTA-treated rats ($P<0.01$). Tumor SI-time curves reflected well the therapeutic response as verified by ex vivo microangiographic and histologic findings. With 1H-MRS, R1 tumor and liver featured a significant choline and lipid peak respectively ($p < 0.0001$), which proved exploitable for monitoring therapeutic response.

CONCLUSION: The present experimental setup enabled in vivo noninvasive longitudinal therapeutic follow-up of post-therapeutic events including vascular shutdown, necrosis, neoangiogenesis and metabolic changes in rodent liver tumors after a single-dose of VTA.

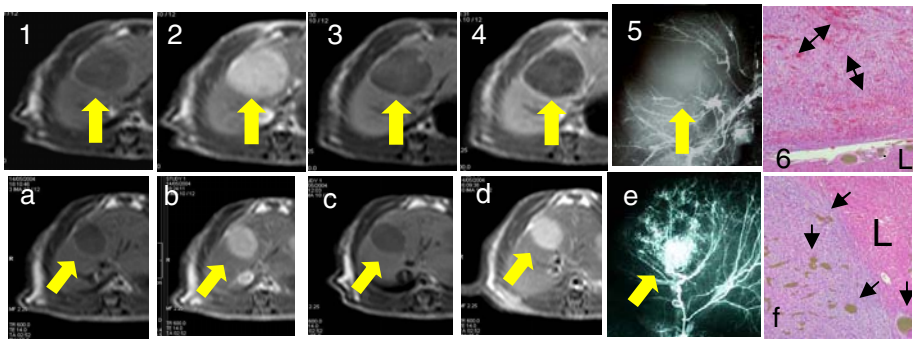

Figure 1. Vascular shutdown effect noninvasively evidenced by contrast enhanced MRI 6 h after treatment of CA-4P (upper row) in comparison with saline control (lower row). Note: 1,2 and a,b baseline pre and post Gd-DTPA; 3,4 and c,d post-treatment pre and post Gd-DTPA; 5 and e microangiography; 6 and f histology (HE stain); large arrows - tumors; double small arrows - thrombosed vessels; small arrows - patent tumoral vessels filled with barium; "L" - normal liver.