Noninvasive Therapeutic Evaluation on Rodent Liver Tumor Treated with Vascular Disrupting Agent: Multiparametric Magnetic Resonance Imaging in Correlation with Microangiography and Histology

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Objectives: To document tumoricidal events after intravenous administration of a vascular targeting agent ZD6126 in rodent liver tumors by using multiparametric magnetic resonance imaging (MRI) and F-18 fluorodeoxyglucose-micro-positron emission tomography (18F-FDG micro-PET) in correlation with postmortem microangiography and histopathology.

Materials and Methods: Forty rhabdomyosarcomas of 8-14 mm in diameter were obtained 16 days after implantation into liver lobes of 20 rats and randomly assigned into control and treated groups. Using a 1.5T Siemens Symphony magnet and a 4-channel wrist coil, T2-weighted imaging (T2WI), pre-contrast T1-weighted imaging (T1WI) and contrast-enhanced T1WI (CE-T1WI), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced MRI (DCE-MRI) were acquired at pre-treatment baseline, 1h, 24h and 48h after iv injection of ZD6126 at 50 mg/kg and vehicle in 15 treated (n = 30) and 5 control rats (n = 10), respectively. Micro-PET was performed at the pretreatment baseline and 24h after the treatment, respectively. In vivo MRI data including signal intensity (SI), tumor volume, DWI-derived apparent diffusion coefficient (ADC), DCE-MRI-derived volume transfer constant per unit volume of tissue, K, and maximal initial slope (MIS) of contrast-time curve (CTC), and PET data including mean standardized uptake value of FDG (SUVmax) and total lesion glycolysis (TLG), were correlated with ex vivo microangiography with digital mammographic unit and micro-computed tomography (micro-CT) and histopathological findings.

Results: ZD6126-treated tumors grew slower than those of controls (P < 0.05) with vascular shutdown evident on CE-T1WI at 1h but more prominent at 24h (Fig. 1, 2). However, enhanced rim occurred in the periphery 48h after treatment, indicating neovascularization (Fig. 2). ADC map enabled distinction between necrotic and viable tumors (Fig. 2, 3). K and MIS significantly decreased at 1h though 24h, and partly recovered at 48h (Fig. 4). SUVmax and TLG significantly reduced at 24h after ZD6126 treatment (P < 0.05) (Fig. 1, 2). ZD6126 selectively targeted at tumor vessels while normal liver was not affected. MRI and PET findings were verified by postmortem microangiographic and histopathological techniques (Fig. 2).

Conclusions: Clinical MRI allowed monitoring of ZD6126-related vascular shutdown, necrosis, and neovascularization of liver tumors in rats. Single dose of ZD6126 appeared insufficient for tumor eradication due to evident peripheral residue and recurrence.

References