Contrast enhanced tumor MRI with a biodegradable macromolecular Gd(III) complex in mice

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Synopsis. Biodegradable macromolecular Gd complex, Gd-DTPA cystine ethyl ester copolymers, was investigated for tumor MR imaging in nude mice bearing MB 231 breast cancer xenographs. The agent produced significantly more contrast enhancement in the blood pool and tumor tissue than a control agent, Gd-(DTPA-BMA). Strong contrast enhancement was observed at 5 minutes postinjection and signal intensity then gradually decreased. Significant contrast enhancement was still visible at 1 hour postinjection.

Introduction. Macromolecular Gd(III) complexes have a long blood pool retention time and have shown superior contrast enhancement in tumor tissues compared to the currently available low molecular weight contrast agents. However, clinical application of macromolecular Gd(III) complexes is limited by their slow excretion and subsequent potential toxicity. Recently, we have designed and developed novel biodegradable polydisulfide based macromolecular Gd(III) complexes for contrast enhanced MR imaging. Here, we report contrast enhanced tumor MR imaging in an animal model with a new biodegradable macromolecular Gd(III) complex, Gd-DTPA cystine ethyl ester copolymers.

Materials and Methods. Gd-DTPA cystine ethyl ester copolymers were prepared by the copolymerization of DTPA dianhydride with cystine ethyl ester, followed by complexation with $GdCl_3$. Animal tumor models were obtained by the subcutaneous implant of breast carcinoma cells MB231 in female nude mice. Mice were anesthetized with an i.m. injection of sodium pentabarbital at a dose of 35 mg/kg. Contrast agents were injected via a tail vein at a dose of 0.1 mmol-Gd/kg. MR images were acquired before contrast and at various time points after contrast on a Siemens Trio 3T scanner. The system body coil was used for RF excitation and a wrist coil was used for RF reception. Imaging parameters used were 2.5 ms TE, 7.4 ms TR, 25º RF tip angle, 120 mm field of view, 0.5 mm coronal slice thickness.

Results. Gd-DTPA cystine ethyl ester copolymers were readily degraded in the incubation with cysteine. The degradation products were characterized with mass spectrometry. The T_1 relaxivity of the copolymers is 13.7 $mM^{-1}s^{-1}$ per Gd(III) ion at 400 MHz, much higher than that of Gd-DTPA cystamine copolymers. Figure 1 shows the 3D MR images of tumor bearing mice contrast enhanced by the macromolecular agent and a control agent, Gd-(DTPA-BMA). Strong contrast enhancement was observed in the heart, blood vessels and tumor at 5 minutes postinjection with the macromolecular agent. Signal intensity was then gradually reduced, but significant contrast enhancement was still observed after one hour. No significant contrast enhancement was observed for the control agent. Images of coronal slices showed that the significant contrast enhancement was observed at the periphery of tumor at 5 minutes postinjection with the copolymers. The signal intensity was then gradually reduced at the tumor periphery and increased in the inner tumor tissue.

Discussion. Introduction of ethyl ester on the polydisulfide agent significantly increased the relaxivity of the biodegradable macromolecular agent, possibly due to the increase of hydrophobicity of the polymers and local rotational correlation time of the macromolecules. The macromolecular agent had a long blood pool retention time and produced significant contrast enhancement in the blood pool and tumor tissue up to one hour postinjection. The longer blood pool retention might be attributed to the slow degradation of disulfide bonds in the copolymers partially due to steric hindrance of ethyl ester groups around the disulfide bond.

Conclusion. The novel biodegradable agent has higher relaxivity, longer blood pool retention time and is more effective for tumor imaging than the control agent. It has a great potential for further clinical development.

References. 1) A. Gossmann, et al. Prostate cancer tumor grade differentiation with dynamic contrast enhanced MR imaging in the rats: comparison of macromolecular and small-molecular contrast media-preliminary experience. Radiology. 213, 265-72, (1999). 2) Z.-R. Lu, et al. Poly(L-glutamic acid) Gd(III)-DOTA conjugate with a degradable spacer for magnetic resonance imaging. Bioconjugate Chem. 14, 715-719 (2003). 3) Z.-R. Lu, et al. Extracellular Biodegradable Macromolecular Gadolinium(III) Complexes for Magnetic Resonance Imaging. MRM, in press.

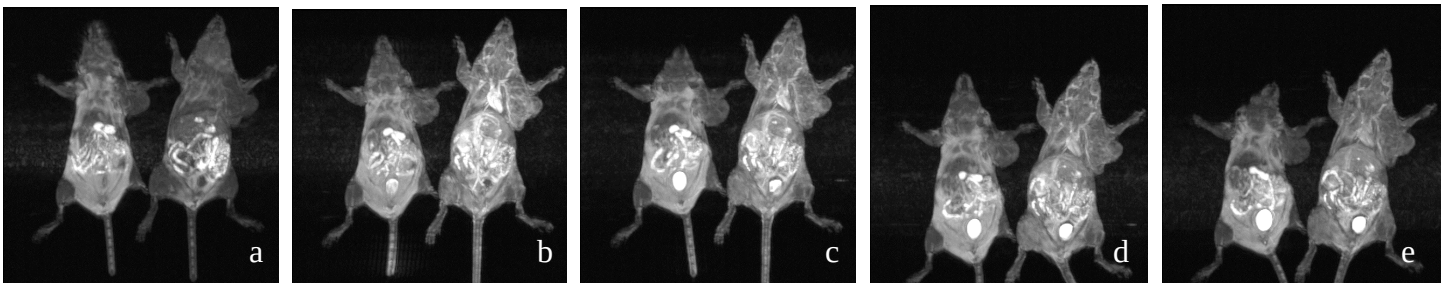

Figure 1. Contrast enhanced 3D (MIP) MR images of mice bearing tumors using Gd-DTPA cystine ethyl ester copolymers (right mouse in figures) and Gd-(DTPA-BMA) (left mouse in figures). The images were taken before contrast (a) and 5, 15, 30 and 60 minutes post-injection.