Comparision of Poly(L-glutamic acid)Gd (III)-DOTA conjugate with Degradable and Non-degradable spacers for Magnetic Resonance Imaging

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Introduction. Clinical applications of macromolecular Gd(III) complexes developed by conjugating Gd(III) chelates to biomedical polymers were hampered by their slow excretion after MRI exam and consequent potential toxicity due to metabolic release of toxic Gd(III) ions. Recently, we have developed disulfide bond-based biodegradable macromolecular Gd (III) complexes that showed great blood pool enhancement with rapid excretion of Gd(III) from body[1-3]. Here we compared the MR contrast enhancement of poly(*L*-glutamic acid) (PGA)-[Gd(III)-DOTA] with degradable spacer cystamine and PGA-[Gd(III)-DOTA] conjugate with a nondegradable spacer 1,6-hexanediamine in mice.

Materials and Methods. PGA-cystamine-[Gd(III)-DOTA] conjugate and PGA-1,6-hexanediamine-[Gd(III)-DOTA] conjugate were prepared by the reaction of amino groups of DOTA-cystamine and DOTA-1,6-hexanediamine with the PGA N-hydroxysucciminide esters, respectively, followed by complexation with $Gd(OAc)_3$. The average molecular weight was determined by size exclusion chromatography. The Gd content was determined by inductively coupled plasma (ICP) spectroscopy. MRI contrast enhancement of the conjugates was evaluated in nude female mice bearing MB231 human breast cancer. MR images were acquired before contrast and at 2, 5, 15, 30, 60 and 1440 (24h) minutes post-injection of the polymer conjugates at a dose of 0.1 mmol-Gd/kg on a Siemens Trio 3T scanner. Imaging parameters were 1.74 ms TE, 4.3 ms TR, 25° RF tip angle, 120 mm FOV, and 1.6 mm coronal slice thickness.

Result. The average molecular weights of PGD-cystamine-GdDOTA and PGA-1,6-hexanediamine-GdDOTA were 70 KDa and 79 KDa , respectively. The Gd content of PGA-cystamine-GdDOTA was 1.15 mmol Gd(III)/g polymer and its T_1 relaxivity was 7.83 $mM^{-1}s^{-1}$. The Gd content of PGA-1,6-hexanediamine-GdDOTA was 0.092 mmol Gd/g polymer and its T_1 relaxivity was 8.33 $mM^{-1}s^{-1}$. Strong contrast enhancement was observed in the heart, aorta and femoral arteries and lasted at least 60 minutes for both agents. After 24 h, no enhancement in the blood pool was observed for PGD-cystamine-GdDOTA and considerable enhancement in the heart was still visible for PGA-1,6-hexanediamine-GdDOTA. Significant contrast enhancement in the liver was also observed for both agents in the first hour post-injection. However, 24 h after the injection, the signal intensity returned nearly to the precontrast level for PGA-cystamine-GdDOTA and PGA-1,6-hexanediamine-GdDOTA still had significant enhancement. The kinetic change of signal intensity in the heart and liver is shown in Figure 1. The contrast enhanced coronal images showing the heart and liver are shown in Figure 2.

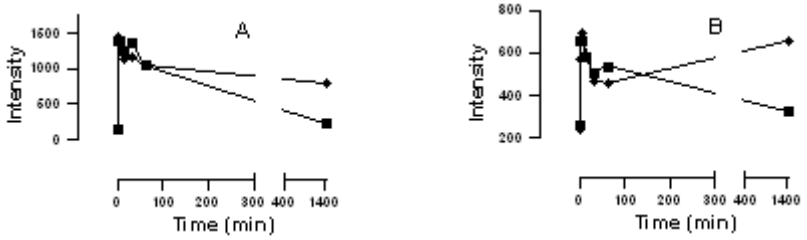

Figure 1. Signal intensity in the heart (A) and liver (B) by PGA- cystamine-GdDOTA (■) and PGA-1,6-hexanediamine-GdDOTA(◆) □

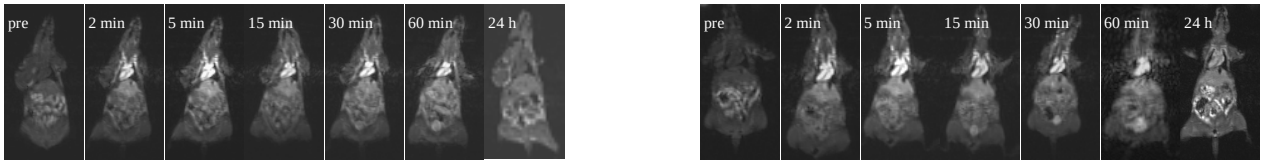

Figure 2. Contrast enhanced MR images with PGA-cystamine-GdDOTA (left) and PGA-1,6-hexanediamine-GdDOTA (right) in mice at a dose of 0.1mmole Gd/kg.

Discussion. The preliminary results showed that both PGA-cystamine-GdDOTA and PGA-1,6-hexanediamine-GdDOTA resulted in strong contrast enhancement in the blood pool for at least 1 hour post injection. Because of the degradation of the disulfide spacer in PGA-cystamine-GdDOTA, the GdDOTA was gradually released from the polymer conjugate and excreted from the body. Consequently, no significant contrast enhancement was observed in the blood pool and liver 24 hours after injection for PGA-cystamine-GdDOTA as compared to PGA-1,6-hexanediamine-GdDOTA. The result indicates that PGA-cystamine-GdDOTA can produce significant in vivo contrast enhancement and Gd chelate from the conjugate can also be readily excreted from the body after released from the conjugate.

Conclusion. The degradable disulfide spacer between Gd(III)DOTA and PGA is crucial for the release and rapid excretion of Gd(III) chelates. PGA-cystamine-GdDOTA is a promising biodegradable macromolecular MRI contrast agent for blood pool imaging including cardiovascular and cancer imaging with minimal Gd tissue accumulation.

Reference. 1) 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). 2) Z.-R. Lu, Extracellular biodegradable macromolecular gadolinium (III) complexes for MRI. Magn. Reson. Med., 51, 27-34 (2004). 3)X., Wang et al. Pharmacokinetics and excretion of biodegradable macromolecular MRI contrast agents. The aaps Journal, Vol 6, issue S1.