Polydisulfide-based Biodegradable Macromolecular Contrast Agents for Dynamic Contrast Enhanced MRI: First Experience with Human Prostate Cancer Xenograft

Y. Feng[1], E-K. Jeong[2], A. M. Mohs[3], L. Emerson[4], and Z-R. Lu[3]

[1]Department of Materials, University of Utah, Salt Lake City, UT, United States, [2]Radiology, University of Utah, Salt Lake City, UT, United States, [3]Pharmaceutics, University of Utah, Salt Lake City, UT, United States, [4]Pathology, University of Utah, Salt Lake City, UT, United States

Polydisulfide-based Biodegradable Macromolecular Contrast Agents for Dynamic Contrast Enhanced MRI: First Experience with Human Prostate Cancer Xenograft

Yi (Harvey) Feng[1], Eun-Kee Jeong[2], Aaron M. Mohs[3], Lyska Emerson[4], Zheng-Rong Lu[3]
Departments of Materials[1], Radiology[2], Pharmaceutics and Pharmaceutical Chemistry[3], Pathology[4]
University of Utah, Salt Lake City, UT 84112

Introduction

DCE-MRI monitors the perfusion of the contrast agent (CA) in tumor to assess its microvasculature for tumor grading and evaluation of efficacy of anti-tumor therapy. Ideal CA for tumor DCE-MRI should have a sufficiently large size that is differentiable by normal and leaky vasculature and could excrete completely out of the body after MRI scan. Polydisulfide-based biodegradable macromolecular CAs (BMCA) are promising for this purpose since initially they have large size providing the advantage of macromolecular CA, and later decrease in size by *in vivo* degradation to facilitate their excretion [1,2]. The current study is the first one to evaluate its performance for DCE-MRI.

Materials and Methods

PCa-2b human prostate cells were inoculated subcutaneous in nude mice. Mouse was placed in a human wrist coil and examined using a Siemens 3T Trio MRI scanner when tumors reached about 1 cm in diameter. Two BMCAs were used: Gd-DTPA cystamine copolymers (GDCC or C, faster degradability) and Gd-DTPA cystine copolymers (GDCP or P). 2 sizes were chosen for each CA: 20 KDa and 70KDa (C20, C70, P20, and P70, respectively). Gd-(DTPA-BMA) (GDB, molecular weight 573 Da) and Albumin-Gd-DTPA (AGD, 92 KDa) were used as controls. A tail vein of the tumor bearing mouse was cannularized for CA administration at a dose of 0.1 mmol/kg body weight (0.03 for AGD). 3D time-of-flight MR image was obtained before DCE-MRI to choose 6 axial slices covering the tumor and the heart. The fast low-angle shot (FLASH) sequence was applied continuously for at least 30 min using the following parameters: TR/TE = 58/4.03 ms, α= 30º, 2 mm slice thickness, one scan average, 3.6 sec for each scan. After the first 12 measurements, a bolus of CA was administered over a period of 10 sec (n=3 for each CA). MR images in DICOM format were analyzed using home- made codes in MATLAB for image analysis. Regions of interests were placed manually in the heart and in the whole tumor for average signal intensity (SI) value at each time point. Peak time (PT) and maximum of the SI time curve of tumor were compared. A two compartment model was used to model CA uptake kinetics in tumor to assess plasma volume (PV), fractional leak rate (FLR), and permeability surface area product (PS) [3].

Results

Fig. 1 (a) to (c) shows the example SI time curves of tumor and the heart enhancement. Baseline SI is subtracted. CA uptake kinetics varies depending on the degradability of BMCA and its molecular weight. Table 1 lists PT and maximum of tumor enhancement. AGD is not included since peak was not achieved during scan time. C70, P20 and C20 provide not only strong enhancement with a wider window for scan, but also reach the maximum enhancement within shorter time (<8 min). Table 2 lists PV, FLR and PS of PCa-2b tumor measured by CAs. The parameters from BMCAs were between AGD and GDB.

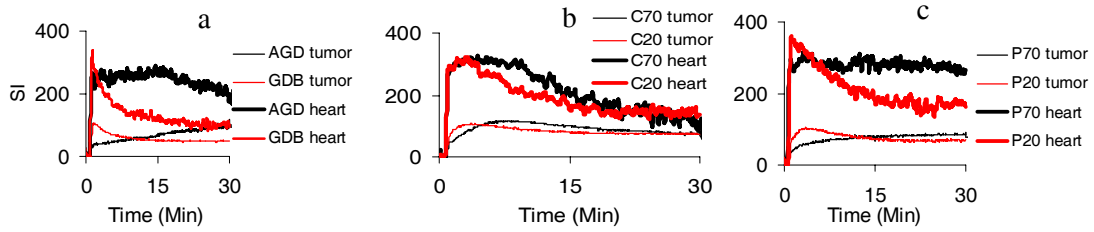

Figure 1. (a) Representative SI for whole tumor and heart of PCa-2b enhanced by: (a) AGD and GDB, (b) C70and C20 and (c) P70 and P20.

Table 1. PT of SI of tumor enhanced by CAs.

	AGD	P70	C70	P20	C20	GDB
PT (Min)		27.2 ± 3.9 *	7.66 ± 0.1*	2.98 ± 0.8	3.1 ± 0.4 *	1.0 ± 0.1
Max ΔSI of tumor	62 ± 13	99 ± 12	114 ± 8	106 ± 23	111 ± 9	105 ± 12

* p<0.05: statistically significantly different between this CA and the one on its right.

Table 2. PV, FLR and PS of PCa-2b tumor measured by CAs.

	AGD	P70	C70	P20	C20	GDB
PV (ml/cc)	0.044 ± 0.006 *	0.066 ± 0.006 *	0.087 ± 0.005	0.117 ± 0.023	0.117 ± 0.010 *	0.166 ± 0.019
FLR (1/hr)	0.49 ± 0.20 *	0.93 ± 0.24 *	4.01 ± 0.14 *	5.58 ± 0.88	4.64 ± 0.86 *	16.38 ± 3.80
PS (ml/hr/cc)	0.022 ± 0.011 *	0.061 ± 0.016 *	0.348 ± 0.031	0.661 ± 0.230	0.539 ± 0.061 *	2.751 ± 0.909

* p<0.05: statistically significantly different between this CA and the one on its right.

Discussion and Conclusions

It is shown in PT, PV, FLR, and PS data that depending on the degradability and molecular weight, BMCA could have different tumor enhancement characteristics. This will be useful since tumor microvasculature varies depending on the origin and grade. In addition to the minimum body accumulation from BMCAs comparing to non-degradable CA, their usage in DCE-MRI for tumor grading and evaluation of efficacy of anti-tumor therapy is promising.

References

[1] Lu ZR, et al. Extracellular biodegradable macromolecular gadolinium(III) complexes for MRI. Magn Reson Med. 51(1):27-34, 2004.

[2] Feng Y, et al. Pharmacokinetics, Biodistribution and Contrast Enhanced MR Blood Pool Imaging of Gd-DTPA Cystine Copolymers and Gd-DTPA Cystine Diethyl Ester Copolymers in a Rat Model. Pharm Res. 23(8):1736-42, 2006. [3] Shames DM et al. Measurement of capillary permeability to macromolecules by dynamic magnetic resonance imaging: a quantitative noninvasive technique. Magn Reson Med. 29(5):616-22, 1993

Acknowledgements Dr. Yong-En Sun, Melody Johnson. NIH R33 CA095873 and R01 EB00489.