Assessment of the antiangiogenic therapy of avastin in an animal colon cancer model with DCE-MRI and a biodegradable macromolecular contrast agent

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Introduction:
Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a non-invasive imaging modality for tumor characterization and evaluating tumor response to anti-cancer therapies [1-2]. Current clinical MRI contrast agents are small molecular contrast agents, which have limitations for accurate and quantitative measurement of tumor vascular parameters due to their non-selective extravasation into the extracellular space of tumor and normal tissues [3]. Although macromolecular contrast agents (MMCs) are effective for tumor characterization and evaluating anticancer therapeutic efficacy in DCE-MRI in preclinical studies, their slow and incomplete elimination limits their development for clinical application. A new class of polysulfide-based macromolecular Gd(III) complexes has been recently developed as biodegradable macromolecular MRI contrast agents to facilitate the excretion of Gd(III) chelates after the MRI examinations [4]. These agents initially behave as macromolecular agents, and then degrade in vivo into low molecular weight Gd(III) complexes that excrete rapidly from the body via renal filtration [5]. In this study, we investigated the efficacy of a promising biodegradable macromolecular contrast agent, Gd-DTPA cystamine copolymers (GDCC), for quantitatively assessing tumor microvascular characteristics and monitoring therapeutic efficacy of antiangiogenic therapy with Avastin® by DCE-MRI.

Materials and Methods:
Athymic nude mice bearing human colon cancer HT-29 xenografts were used as the animal tumor model in the study. The animals were randomly assigned to two groups (one for DCE-MRI with GDCC and the other for Gd(DTPA-BMA) and treated with Avastin®. The mice were treated with Avastin® three times in a week via intraperitoneal injection. DCE-MRI was performed in the animal model with GDCC-40 (MW = 40 kDa) and Gd(DTPA-BMA) before and after the treatment with Avastin®. The DCE-MRI data were analyzed with a two-compartmental model to estimate tumor vascular parameters, endothelial transfer coefficient (Ktrans) and vascular volume fraction (fV). The vascular parameters determined with both agents before the treatment was used as the baseline values and the parameters at 36 h and 7 days after the treatment were compared to the baseline to evaluate the therapeutic efficacy. Tumor size was also monitored during the experiments. Statistical analysis was performed using a paired two-tailed Student’s t-test.

Results:
Figure 1 shows the tumor growth curve before and after the treatment with Avatin®. The treatment with Avatin® initially inhibited tumor growth and tumor then started re-growth at a slower rate after the treatment. Figure 2 shows the tumor vascular parameters, Ktrans and fV, estimated by DCE-MRI with GDCC-40 and Gd(DTPA-BMA) before and after the treatment. Both Ktrans and fV determined at 36 h after the first administration with GDCC-40 significantly decreased as compared to those before the treatment (P < 0.05). At 7 days after 3 doses of Avastin®, however, the parameters increased and were not significantly different from the baseline values (Figure 2A). The results correlated well to tumor growth. In comparison, the vascular parameters estimated from Gd(DTPA-BMA) did not show any significant difference before and after the treatment (Figure 2B).

Conclusions:
DCE-MRI with the biodegradable macromolecular contrast agent GDCC-40 can effectively evaluate the therapeutic efficacy of anti-angiogenic therapy. The biodegradable macromolecular contrast agent has a potential to be used to monitor therapeutic efficacy of an anti-angiogenic therapeutics based on tumor vascular parameters.

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