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 (MMCAs) 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 clinic application. A new class of polydisulfide-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 (K^{trans}) and vascular volume fraction (f^{PV}) for each contrast agent. 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 Avstin® initially inhibited tumor growth and tumor then started re-growth at a slower rate after the treatment. Figure 2 shows the tumor vascular parameters, K^{trans} and f^{PV}, estimated by DCE-MRI with GDCC-40 and Gd(DTPA-BMA) before and after the treatment. Both K^{trans} and f^{PV} determined at 36 h after the first administration estimated 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).

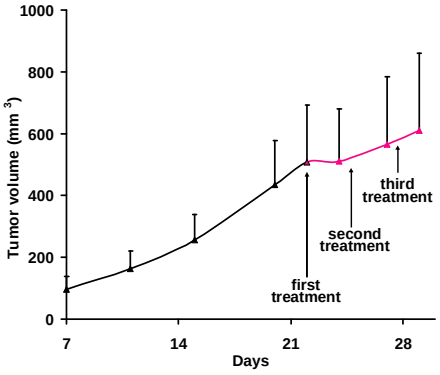

Figure 1. Tumor growth curve before and after the treatment with Avastin®.

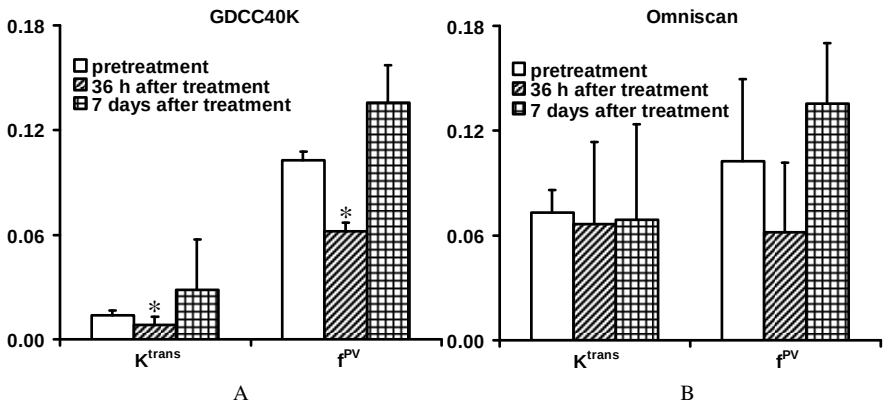

Figure 2. Graph shows change in K^{trans} and f^{PV} for GDCC40K (A) and Omniscan (B) before and after Avastin administration. *: P<0.05.

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.

References:

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