Differential sensitivity to vascular permeability using low-MW and high-MW contrast agents for DCE-MRI

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Introduction

The clinically approved, low-MW (<1000 Da) Gd chelates are often used in DCE-MRI for the diagnosis and detection of response to therapy, especially with anti-vascular and anti-angiogenic agents, and can facilitate the clinical decision-making process. Macromolecular contrast materials (MMCM; >30,000 Da) in which multiple Gd chelates are conjugated to a macromolecular protein (e.g., albumin) or polymers have been designed for prolonged retention in the circulation. The MMCM act as blood pool agents and allow more accurate quantification of tumor vasculature as well as measurement of physiologically relevant parameters (1, 2). Using macromolecular DCE-MRI and immunohistochemistry we recently demonstrated that the anti-vascular function of the PDGFR inhibitor imatinib (alone or with paclitaxel) in a prostate cancer bone metastases model resulted from reduced VEGFR signaling (3). The purpose of this study was to compare the sensitivity of low-MW and high-MW contrast materials to anti-vascular therapy with PDGFR inhibitor by sequential DCE-MRI before and after short-term treatment in the same animal.

Methods

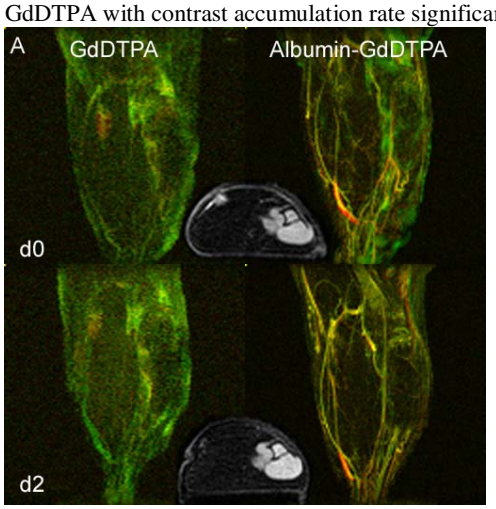
Tumor model: Prostate cancer bone metastasis model was initiated by intratibial injection of PC-3MM2 cells (1x105 cells/20 µl) in male CD-1 nude mice using a 27-gauge needle (4). Mice were imaged weekly and then before (d0) and at the end of 2-days (d2) of drug therapy.

Combined anti-vascular drug therapy (4) started ~one week after tumor exited the bone (d0) and consisted of imatinib, (provided by Novartis Pharma, Basel, Switzerland; 50 mg/kg; ip at d0, d1 and d2) and Paclitaxel (Bristol-Myers Squibb, Princeton, NJ; 8 mg/kg; ip once at d0).

MRI experiments: MR images were acquired on a 4.7T Biospec (Bruker Biospin, Billerica, MA) using micro-imaging gradients and a purpose-built knee coil. T2-fSE: TR 4500 ms, TE 15.6 ms, 2 averages, matrix 256x192, FOV 30x30 mm, slice thickness 1 mm. 3D-fSPGR: precontrast flip angles 10, 15, 35, 50, 70 degrees; postcontrast flip angle 35 degrees, TR 10 ms, TE 1.23 ms, 2 averages. Matrix 128x96x8 and 128x128x32, FOV 20x20x10 and 20x20x20 mm, acquisition time 7.7 and 81.92 s for GdDTPA (938 Da; gadopentetate dimeglumine, Magnevist®; Berlex, Germany; 0.2 mmol/kg iv) and albumin-GdDTPA ((3); ~85000 Da; 350 mg/kg iv) respectively. Signal intensity was converted to R1 values as described (3).

Results

Mice were imaged weekly to monitor tumor growth. Anti-vascular drug therapy was started one week after the tumor was first observed outside the bone (typically 4-5 weeks after tumor inoculation). Short-term interventional anti-vascular therapy combining imatinib and paclitaxel resulted in reduced extravasation of the high-MW albumin-GdDTPA but not of the small GdDTPA (Fig1A). Quantitative analysis indicated that the initial contrast enhancement ($dR1_0$; representing the vascular phase) and the initial rate of contrast accumulation (dR1/dt; representing vascular permeability) slightly increased at the end of 2-days anti-vascular treatment for GdDTPA, whereas both parameters were decreased for albumin-GdDTPA with contrast accumulation rate significantly reduced by 37% (two-tailed paired t-test p=0.003; n=3; Fig1B).



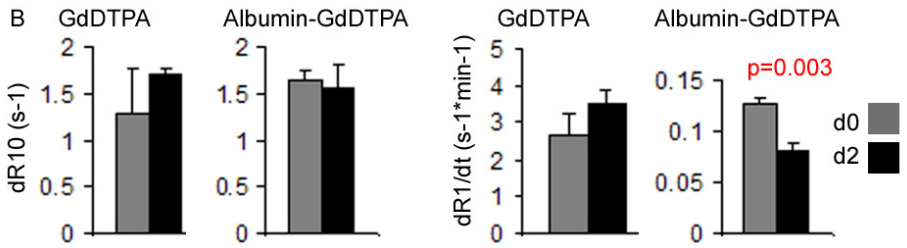


Figure 1. A) Representative results for one mouse, before (d0) and after (d2) anti-vascular treatment, showing coronal maximal intensity projections of the 3D-fSPGR datasets, presented as overlay of 7 s and 1.5 min (red) and 70 s and 30 min (green) post injection of GdDTPA and albumin-GdDTPA respectively. Also included are pre-contrast axial T2W images. Note that injection of albumin-GdDTPA was performed 3-4 hr after injection of GdDTPA, to allow complete clearance of the first agent. B) Quantitative results (n=3): initial contrast enhancement ($dR1_0$) and initial rate of contrast accumulation (dR1/dt) calculated for the first 77 s (GdDTPA) and 15 min (albumin-GdDTPA) post-contrast.

Discussion

These initial results suggest that the macromolecular contrast material albumin-GdDTPA is more sensitive than the small GdDTPA to the vascular changes induced by the anti-PDGFR therapy in this tumor model. This differential sensitivity reflects differences in pharmacokinetics and mechanism of vascular permeability. Small molecules freely diffuse across the vessel wall whereas macromolecules are transported by an active trans-endothelial transport mechanism regulated by permeability factors (i.e., VEGF, histamine) (5). Thus these findings suggest that development of MMCMs for clinical use and their incorporation in clinical DCE-MRI is crucial in order to provide more sensitive and selective detection of early response to some anti-vascular therapies, prior to actual decrease in vessel density.

References

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