Macromolecular Versus Small Molecular MRI Contrast Media for Monitoring Anti-angiogenic Drug Effect of Bevacizumab on Experimental Human Breast Cancer Xenografts

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Purpose: To compare macromolecular (MMCM) versus small molecular contrast media (SMCM) for their suitability to monitor early anti-angiogenic drug effect of bevacizumab on experimental human breast cancer xenografts in dynamic MRI assays of endothelial permeability in a tandem experiment.

Methods and Materials: Subcutaneous human breast cancer xenografts (MDA-MB-435) were implanted into 12 athymic rats and imaged by dynamic contrast-enhanced MRI at 2.0T. Measurements of endothelial permeability were performed using the MMCM prototype albumin-$(Gd\text{-}DTPA)_{27}$ (1) with a molecular weight (MW) of 92 kDa rats followed by an injection of the SMCM Gd-DTPA with a MW of 0.6 kDa in the same experiment. Rats were imaged at baseline and 24h after a single dose intraperitoneal injection of bevacizumab (1mg) to generate quantitative MRI estimates of tumor microvessel permeability (K^{PS}; µl/min·100cm^3) using a 2-compartment kinetic model (2).

Results: Dynamic MRI assays of tumor endothelial permeability revealed a significant decrease of the endothelial transfer coefficient K^{PS} from baseline to 24h after treatment using the MMCM albumin-$(Gd\text{-}DTPA)_{27}$ (31.0±14.8 to 0µl/min·100cm^3, $p<0.05$). On the contrary, no significant effect on tumor endothelial permeability was detected when using the SMCM Gd-DTPA for enhancement (28,600±9,700 to 37,500±10,400µl/min·100cm^3, $p>0.05$) in the same experiment.

Conclusion: In MRI assays of endothelial permeability, prototypic MMCM albumin-(Gd-DTPA) proved to be clearly superior to the SMCM Gd-DTPA for the detection of early anti-angiogenic effect of bevacizumab on experimental human breast cancer xenografts. No effect was detected when using Gd-DTPA for enhancement. In dynamic contrast-enhanced MRI assays of endothelial permeability, the molecular weight of the applied contrast agent seems to be of pivotal importance.

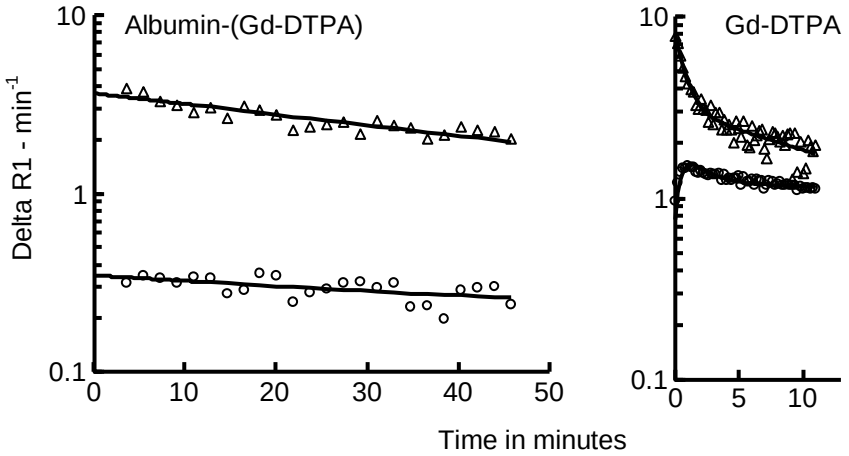

Figure1: Tandem experiment. Representative fits (solid lines) of compartmental model to delta R1 data from blood (Δ) and tumor (O) following injection of albumin-(Gd-DTPA) followed by an injection of Gd-DTPA 75 minutes later. During the interval between the two experiments, a new "precontrast R1" is measured before the Gd-DTPA injection.

References:

1. Van Dijke CF et al Acad Radiol 9 (Suppl 1) 2002; 257–260.
2. Cyran CC et al J Magn Reson Imaging. 2008; 27(3):581-9.