Dynamic Contrast-Enhanced (DCE)-MRI with Gadobutrol for Monitoring Sorafenib Effect on Experimental Prostate Carcinomas

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Purpose: To investigate and quantify the anti-angiogenic effect of the multikinase inhibitor Sorafenib on experimental prostate carcinomas in rats with Gadobutrol-enhanced DCE-MRI assays of endothelial permeability and tumor perfusion.

Methods and Materials: A total of 20 Copenhagen rats implanted with subcutaneous prostate carcinoma allografts (MLLB-2) were imaged at baseline and after one-week by dynamic MRI at 3T following enhancement with the small molecular contrast agent Gadobutrol (Gadovist®, Bayer Schering AG, Berlin, Germany). The treatment group (n=10) received daily applications of Sorafenib (10mg/kg bodyweight) via gavage; the control group (n=10) was treated with volume equivalent applications of the solvent of Sorafenib, Cremophor/Ethanol. Quantitative MRI estimates of tumor microvessel permeability (endothelial transfer constant K^{PS}, ml/100ml/min) and tumor plasma flow (tumor perfusion PF; ml/100ml/min) were calculated using the PMI 0.4 software based on a two-compartment kinetic model (1).

Results: Sorafenib significantly suppressed tumor perfusion in prostate carcinoma allografts over the treatment course of one week (PF baseline 47,934 ± 36,855 to Day 7 24,374 ± 18,494 ml/100ml/min). No significant effect was observed on tumor endothelial permeability in the Sorafenib-treated therapy group from baseline to day 7 (K^{PS}baseline=6.09 ± 4.06 vs. K^{PS}Day7 4.72 ± 2.45 ml/100ml/min, $p>0.05$), as assayed by Gadobutrol-enhanced MRI. In the control group (n=10) treated daily with volume equivalent applications of the solvent of Sorafenib, Cremophor/Ethanol, tumor perfusion increased significantly over the course of one week (PF baseline 37,635 ± 12,327 vs. Day 7 49,847 ± 14,981 ml/100ml/min, $p<0.05$). No significant alteration of endothelial permeability was observed in the control group.

Conclusion: Tumor perfusion (ml/100ml/min), as assayed by Gadobutrol-enhanced DCE-MRI can be considered a promising non-invasive surrogate parameter for monitoring anti-angiogenic effects of Sorafenib on an individual tumor basis. As indicated by previous studies (2), small molecular contrast media does not seem to be applicable for non-invasive and reproducible measurements of tumor endothelial permeability by DCE-MRI.

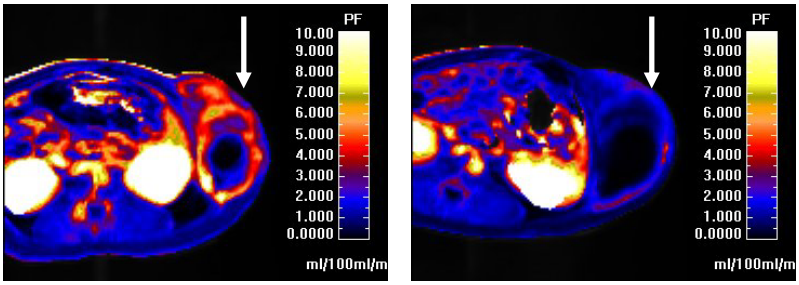

Figure 1. Therapy group perfusion maps depict the significant decrease of tumor perfusion (ml/100ml/min) in subcutaneous prostate carcinomas (white arrows) from baseline to day 7 following a one-week, daily treatment course of Sorafenib (10mg/kg) via gavage.

References:

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