Dynamic Contrast-Enhanced (DCE)-MRI Enhanced With Macromolecular Contrast Media 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 DCE-MRI assays of endothelial permeability and tumor vascularity.

Methods and Materials: A total of 16 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 prototype macromolecular contrast agent albumin-$(Gd\text{-}DTPA)_{35}$. The treatment group (n=8) received daily applications of Sorafenib (10mg/kg bodyweight) via gavage; the control group (n=8) 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 vascularity (blood volume; %) were calculated using the PMI 0.4 software based on a two-compartment kinetic model (1).

Results: Sorafenib significantly suppressed endothelial permeability and blood volume in prostate carcinoma allografts over the treatment course of one week. In Sorafenib-treated tumors (n=8) the transfer constant yielded a significant decrease in endothelial permeability from baseline to day 7 (K^{PS}baseline=0.62 ± 0.20, K^{PS}day7=0.08 ± 0.09; $p<0.01$). The blood volume in Sorafenib-treated tumors decreased significantly over the treatment course (BV baseline=5.1 ± 1.0, BV day7=0.56 ± 0.48; $p<0.01$). No significant alteration of endothelial permeability or tumor vascularity was observed in the control group (n=8).

Conclusion: Sorafenib, a known inhibitor of angiogenesis in renal and liver cancer (2), significantly reduced endothelial permeability and tumor vascularity in a prostate cancer model as assayed by dynamic MRI enhanced with macromolecular contrast media. Pending further investigations, DCE-MRI enhanced with macromolecular contrast media may prove as a valuable tool for monitoring the anti-angiogenic effect of Sorafenib on an individual patient basis.

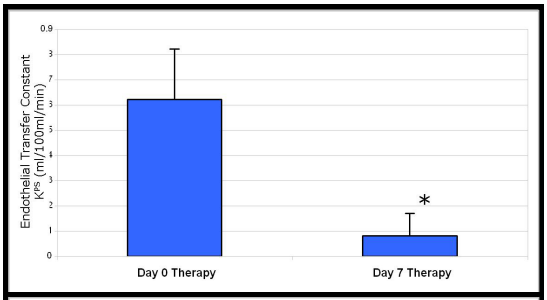

Figure 1. Depicts the significant ($p<0.01$) decrease of endothelial permeability in prostate carcinoma allografts following a daily, one-week treatment course of Sorafenib via gavage.

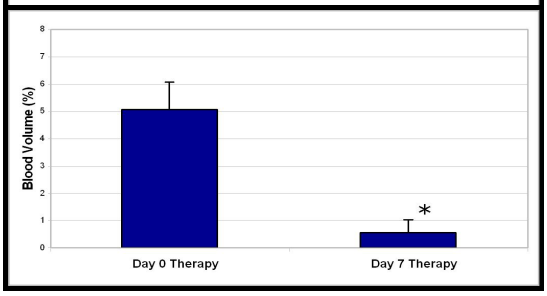

Figure 2. Depicts the significant ($p<0.01$) decrease of tumor vascularity in prostate carcinoma allografts following a daily, one-week treatment course of Sorafenib via gavage as assayed by dynamic, contrast-enhanced MRI and macromolecular contrast media.

References:

1. Sourbron S, Dujardin M, Makkat S, Luypaert R. Pixel-by-pixel deconvolution of bolus-tracking data: optimization and implementation. Phys Med Biol 2007; 52:429-447.
2. Chiou JF, Tai CJ, Wang YH, Liu TZ, Jen YM, Shiau CY. Sorafenib induces preferential apoptotic killing of a drug- and radio-resistant Hep G2 cells through a mitochondria-dependent oxidative stress mechanism. Cancer Biol Ther 2009; 8.