Preclinical Therapeutic Sequencing using a Dual-Tracer Multi-Animal DCE-MRI Platform

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Introduction

Dynamic contrast-enhanced (DCE)-MRI is a functional imaging method that is often used to quantify changes in tumor microvasculature in small animal models of cancer. Unfortunately, the relatively long imaging protocol results in high costs for imaging, a limited number of animals that can be scanned over a given time interval, and logistical complications that can dominate the design of an experiment that is intended to test a biomedical hypothesis. We have previously demonstrated a multi-animal imaging system to enable simultaneous DCE-MRI measurements from up to four animals at a time [1] with no sacrifice in image quality when compared to serial single-animal imaging. Higher throughput facilitates the design of preclinical studies with more and larger groups of animals that are tested over a shorter interval than could previously be practically achieved. This imaging platform has been used to compare response to combinations of radiation therapy (XRT) and PX-478, a novel selective HIF-1α inhibitor currently in Phase I clinical trial, in a murine model of pancreatic cancer.

Methods

All experiments were approved by our Institutional Animal Care and Use Committee, which is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. All data was acquired using a 4.7T Biospec USR47/40 small animal imaging system (Bruker Biospin MRI, Billerica, MA) with four receive channels. All data analysis was performed using Matlab (The Mathworks, Natick, MA).

Six groups of eight severe combined immunodeficient mice bearing subcutaneous Panc-1 tumors were administered either: 1 Gy XRT daily for 5 days; 20 mg/kg PX-478 daily for 5 days; concurrent PX-478+XRT with PX-478 (as above) given 4 hours before XRT (as above) daily for 5 days; PX-478 for 5 days followed by XRT for 5 days; XRT for 5 days followed by PX-478 for 5 days; or sham irradiation. DCE-MRI measurements were made at baseline before therapy, on the 5th day of the first of sequential therapies when appropriate, and three and ten days after completion of therapy. Tumor volume was measured twice weekly using electronic calipers.

A dual-tracer DCE-MRI protocol [2,3] was used to evaluate changes in tumor microvasculature. Animals were anesthetized in 0.5-2% isoflurane in oxygen, placed head first and prone on a 4-animal positioning sled, and monitored using respiratory bellows. Four linear birdcage coils were arranged in a linear fashion [1]; transmit power was split equally among all channels and was isolated from receive using four actively-controlled T/R switches. Coronal FLASH images were acquired to verify positioning of all animals. T1- and T2-weighted axial and coronal spin-echo scans were used to visualize tumor and a saturation-recovery sequence was used to measure T1 of tumor tissue before administration of contrast. 62 repetitions of a T1-weighted FSPGR sequence were used to acquire dynamic data from eight 1mm slices over a 10-minute period. After one minute of baseline scans, 0.2 mMol/kg PG-Gd-DTPA [4] were injected to saturate the vascular space. Five minutes later 0.2 mL/kg Gd-DTPA was injected. Mean values for DCE-MRI biomarkers of permeability and vascular volume fraction were compared using the Wilcoxon rank-sum test.

Results & Discussion

DCE-MRI estimates of vascular volume fraction reveal statistically significant differences between control and animals exhibiting durable response (PX-478+XRT) as early as +3d after completion of therapy ($p < 0.05$). Indicators of vascular volume fraction and permeability (Fig 1) are both different by +10d after completion of therapy ($p < 0.01$), preceding statistically significant differences in tumor growth curves (Fig 2; $p > 0.05$ at +10d). These results not only inform on best use of a clinically relevant therapeutic agent, but also suggest that DCE-MRI may provide an early indication of response to therapy. The dual-tracer multi-animal DCE-MRI system enables preclinical evaluation of novel therapeutic regimens using large cohorts of animals.

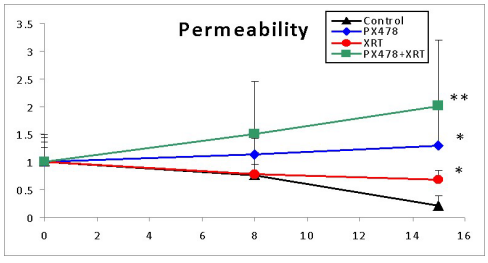

Figure 1: Estimates of vascular permeability are clearly differentiable by +10d after therapy.

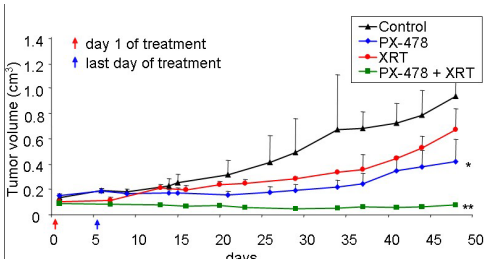

Figure 2: Tumor growth curves for control, single-agent, and combined therapies.

References

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