DCE-MRI for evaluation of response to gefitinib: comparison of two treatment regimens in a breast cancer model

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Introduction: Dose scheduling of combined cancer therapies may play an important role in treatment efficacy. It has been shown in preclinical studies that gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, administerd as a 2-day pulse prior to paclitaxel resulted in greater tumor growth inhibition than continuous gefitinib or either agent alone. The mechanism of the improved response to the pulsed regimen is not known. One hypothesis is that it may be mediated through transient effects on tumor vasculature. DCE-MRI allows the non-invasive assessment of tumor microvascular parameters such as partial plasma volume (fPV) and endothelial transfer constant K^{ps} [1].This study utilized DCE-MRI to determine if the 2-day pulsed gefitinib dosing regimen had differential effects on tumor vasculature or other MR-measured parameters compared to continuous (daily) gefitinib dosing.

Methods: Female nude mice were implanted with the human breast cancer line BT474, a Her2/neu over-expressing variant. Tumors were volume matched and baseline images (day 0) were acquired when tumors reached an average volume of 400 mm^3. Treatment was initiated after baseline imaging. Three treatment groups were studied: C=vehicle control; GP=two day pulse gefitinib (1000 mg/kg on day 2 and day 3); and GC=continuous gefitinib (150mg/kg daily from day 0 to day 9). To evaluate early (shortly post-2-day pulse) and late-treatment effects DCE-MRI was performed on day 4 and day 9. Prior to imaging, mice were anesthetized with 1.5% isoflurane. For DCE-MRI studies, mice were injected i.v. with 0.03 mmol/kg albumin $GdDTPA_{30}$. Imaging was performed on a 1.5T GE Signa scanner (General Electric Medical Systems, Milwaukee, WI) using a conventional wrist coil and customized animal holder. Initial tumor $T1_0$ was measured using a 3D variable flip angle fast gradient echo technique [2]. Contrast-enhanced imaging was performed using a coronal T1-weighted 3D gradient echo sequence (TR/TE10.4/4.2 ms, FOV 10 cm, matrix 256 x 192, slice thickness 1.0 mm, 1 NEX). A unidirectional two-compartment model [3] incorporating the individual arterial input function (AIF) for each mouse was utilized to calculate K^{ps} and fPV for each tumor.

Results: The tumor MRI parameters evaluated for each treatment group are shown in Table 1. Differences between the two treatment groups were observed at early and late imaging time points. The GP group showed a transient significant decreases (day 4) in mean tumor K^{ps} ($p<0.005$), $T1_0$ ($p<0.05$) accompanied by a decrease in volume (-25%) and an increase in fPV. In contrast, the GC group showed continuous trends over the course of the study, with tumor volume and fPV increasing and $T1_0$ and K^{ps} decreasing with time. Additionally, when all data were pooled, a correlation was found between change in tumor volume and K^{ps} (Figure 1). Both gefitinb treatment groups were characterized by negative K^{ps} values post-treatment that were not observed in control tumors for the experiment.

(mean ± SD)	Tumor Vol (# voxes l)	$T1_0$ (ms)	K^{ps} (ml/100 g/min)	fPV (%)
Controls, 0d (n=2)	3677±703	1217±49	0.0275±0. 0007	1.15±0.2 1
Controls, 4d (n=2)	5517±272	1066±55	0.0055±0. 0078	0.85±0.0 7
G pulse, 0d (n=4)	3653±724	1226±107	0.0203±0. 0075	1.40±0 .30
G pulse, 4d (n=4)	2729±703	998±37	-0.0135±0. 0107	1.95±0.5 3
G pulse, 9d (n=2)	3616±631	1160±116	0.0670±0. 0651	1.65±0.9 2
G continuous, 0d (n=4)	3412±1281	1442±250	0.0197±0. 0032	0.93±0.3 2
G continuous, 4d (n=4)	4251±1328	1132±61	-0.0010±0. 0115	1.15±1. 03
G continuous, 9d (n=3)	5518±895	1096±149	-0.0087±0. 0301	1.57±0.7 8

Table 1

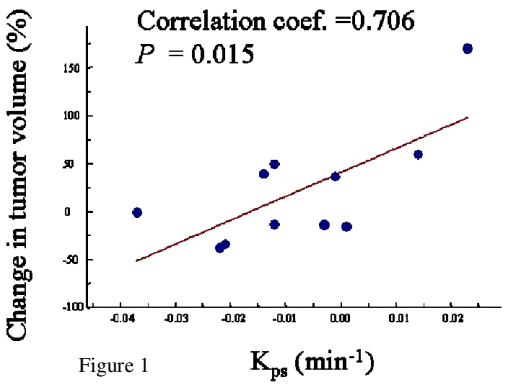

Figure 1

Discussion: Results of DCE-MRI studies in mice receiving different gefitinib dosing regimens (2-day pulse or continuous dose) demonstrated differences in tumor MR-measured parameters between the two treatment groups The significant changes in tumor $T1_0$ and K^{ps} in addition to MR volume post 2-day pulse suggests these measures may be sensitive to differential response to gefitinib. Analyzing the DCE-MRI data with the unidirectional two-compartment model resulted in negative K^{ps} values in some treated tumors. This result needs to be further investigated. This preliminary work indicates that DCE-MRI may provide useful surrogate markers to aid in assessing the effects of treatment timing and dose for combined anti-cancer drug strategies.

References: [1] Padhani. Br J Rad 2003;76:20-40. [2] Fram et al. MRM 1987;5:201-8.[3] Tofts et al. MRM 1995; 33:564-668.

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