DCE-MRI Evaluation of Eribulin Mesylate in MX-1 Triple Negative Human Breast Cancer Mouse Xenograft Model

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Introduction: Eribulin mesylate (ERI), a synthetic macrocyclic ketone analog of the marine sponge natural product halichondrin B, is an approved third line therapy for breast cancer(1). The goal of this work was to use DCE-MRI to evaluate eribulin's effect on tumor vasculature and growth in a human breast cancer mouse xenograft model (MX-1). The effects of eribulin on the MX-1 tumors are compared to capecitabine, a cytotoxic known to interfere with DNA and RNA synthesis.

Methods: All procedures were approved by the Eisai IACUC committee. DCE-MRI scanning was conducted on a Bruker 70/20 USR magnet. Mice with MX-1 flank tumors were anesthetized with isoflurane and positioned with the tumor centered over the surface coil (20mm, Bruker) and centered in an 86mm quadrature volume coil (Bruker). Isoflurane via nose cone was maintained at 2% during scanning, while body temperature and respiratory rate were monitored. Anatomic images were acquired with RARE: 10.5/2088msec TE/TR; 256x256 matrix; 3.5x3.5cm FOV; NA 3; 1.5mm slices covering the whole tumor. DCE acquisition was performed using a GE FLASH with the same geometry as the anatomic scan: FA 60; 2.1/80 TE/TR; 128x128 matrix; NA 2. Magnevist, 0.3mmol/kg bolus (0.1ml saline flush) was injected via tail vein at 1-1.5 minutes after beginning the acquisition. Total acquisition time was ~ 15min. Imaging was conducted on day -1 (baseline) and again at 6 hours, day 2 and day 5 post-dosing. Mice were randomized into treatment groups based on K_{trans} values calculated at baseline data. The ERI group (n=5) received 3 mg/kg eribulin i.v. (MTD) on day 0. The CAP group (n=5) received 540mg/kg capecitabine p.o. daily (MTD) from day 0 to day 5. A VEH group (n=5) was dosed with saline. Voxel-wise baseline T1 values were estimated according to the method of Fram, et al (2) from measured signal intensities acquired using a FLASH sequence at five different flip angles. Along with the Gd relaxivity constant, these T1 estimates were used to estimate [Gd] concentration in each voxel at each time point. Plasma concentration was estimated from the model input function of Checkley, et al (3). K_{trans} and v_e were estimated by fitting the Kety-Tofts model using the plasma and voxel-specific tissue concentration curves as input.

Results/Discussion: CAP treatment, at the dose of 540mg/kg, did not produce any changes different from vehicle treatment in the MX-1 tumors in our study. However, at 6 hours post dose, K_{trans} in the tumor was reduced in the ERI group (shown in whole tumor), but remained unchanged in the VEH group (fig 2). K_{trans} in the ERI group increased at the day 2, relative to VEH, and day 5 compared to baseline, reaching statistical significance by day 5 (fig 1 and 2, $p<0.05$). Tumor K_{trans} remained unchanged or went down slightly in the CAP and VEH groups by day 5 (fig 1 and 2). In addition, while v_e (extracellular/extravascular space) in the tumor rim of CAP and VEH tumors remained unchanged over the 5 days, the ERI group tumors showed an upward spike at 6hrs, and then trended downward at day 2 and day 5 (fig 3). The decrease in K_{trans} along with increased v_e at 6hr in the ERI group show acute vascular activity. These data were confirmed by a significant decrease in Hoescht staining at 6hrs following a 3mg/kg dose in MX-1 mice tumors($p<0.05$ VEH vs ERI) (These in-vivo Hoescht data are currently under review as part of an abstract submitted to AACR 2013). The significant rise in K_{trans} values at day 5 in the ERI group could possibly indicate recovery of vasculature function and then normalization of the vasculature leading to increased perfusion throughout the tumor (5). While more work is needed to confirm this hypothesis, vascular normalization may provide an advantage by normalizing pressure, oxygenation, and perfusion, thereby making the tumor more vulnerable to cytotoxic insults (5). These DCE-MRI data suggest that in addition to eribulin's known cytotoxic effects, eribulin treatment may have the potential to also normalize tumor vasculature in triple negative breast cancer models.

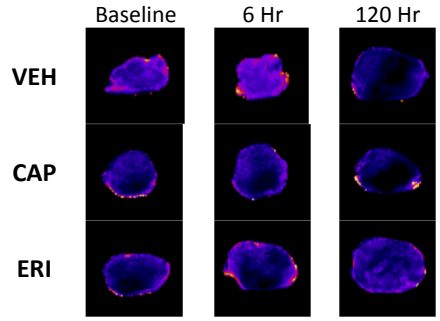

Fig 1. Representative K_{trans} maps from a single tumor slice.

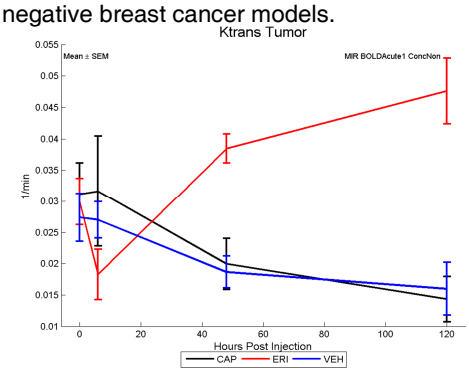

Fig 2. K_{trans} values for each group over the study course.

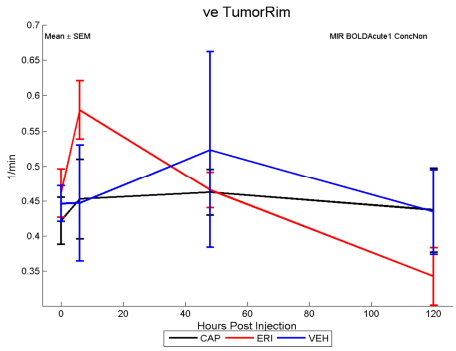

Fig 3. Extracellular/Extravascular space in the tumor rim for each group.

References: 1. Hyuck etal. Nature Rev Drug Disc (2011)10:73; 2. Fram etal. Magn Reson Imaging (1987)5(3):201; 3. Checkley etal. Br J Cancer(2003)89; 4. Galbraith etal. 37th Soc for Clin Onc 2001b; 5. Jain RK. Science(2005)307:58.