Early ADC changes following treatment with doxorubicin containing anti-HER2 immunoliposomes predict tumor growth inhibition

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Background: The development of therapies targeted to specific cell surface receptors has the potential to increase the efficacy and selectivity of cancer treatment. The HER2/neu (erB2) protein is a readily accessible cell surface receptor that is overexpressed in 20-30% of breast and ovarian cancers, as well as in other carcinomas; and its overexpression is associated with poor prognosis. Anti-HER2 doxorubicin immunoliposomes, constructed by conjugation of anti-HER MAb fragments to sterically stabilized liposomes, have shown increased anti-tumor activity compared to other forms of doxorubicin [1]. The ability to non-invasively assess the anti-tumor effects of targeted agents can aid in the development and assessment of new therapeutics. Previous work has shown that the apparent diffusion coefficient of water (ADC) measured by diffusion-weighted MRI can be a sensitive indicator of early treatment response [2]. The goal of this work was to evaluate effects of the targeted tumor therapy doxorubicin containing anti-HER2 immunoliposomes (dox-ILs) and a conventional therapy (free doxorubicin) on tumor volume and apparent diffusion coefficient (ADC) in a mouse model of human breast cancer.

Methods: Doxorubicin encapsulating anti-HER2 targeted immunoliposomes (dox-ILs) were prepared (HSPC/Chol/PEG-DPSE, mean diameter ~75nm) as previously described [3]. Immunoliposomes were targeted via an F5 scFv antibody fragment. Nude mice were implanted with the HER2/neu over-expressing human breast cancer line BT474. Mice in the three treatment groups were dosed one time, immediately post-baseline MRI: 1) control group (saline, n=4); 2) dox-IL group (7.5 mg/kg doxorubicin, n=2); and 3) free doxorubicin (7.5 mg/kg doxorubicin, n=2). Tumor-bearing mice were imaged in pairs prior to, and at 1 week and 2 weeks post-treatment. During imaging, mice were anesthetized with 1.5% isoflurane. 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. A 3DFGRE image was acquired at each time point (TR/TE=17/4.2ms, FOV=10 cm, matrix=256x256) for determination of tumor volume. Diffusion weighted images were acquired using a single shot fast spin echo sequence (TR/TE=27/8ms, FOV=10 cm, b=0,600 s/mm^2). Tumor regions of interest were drawn on 3D images and the volumes and ADC values of those regions were then calculated.

Results: The mean tumor volume of each group at each time point is shown in Figure 1. The control tumors continued to grow, while the free dox and dox-IL groups both showed growth inhibition at 2 weeks. At this time the mean tumor volume in the free dox group

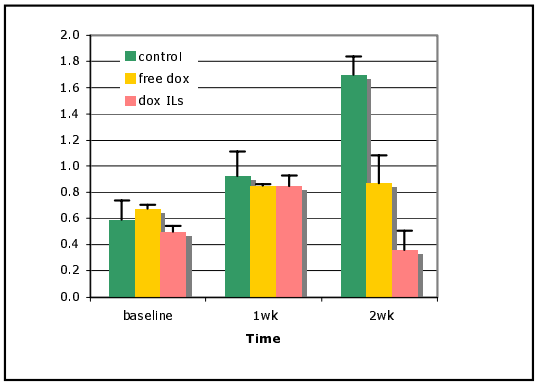

Figure 1. Tumor volumes for three treatment groups

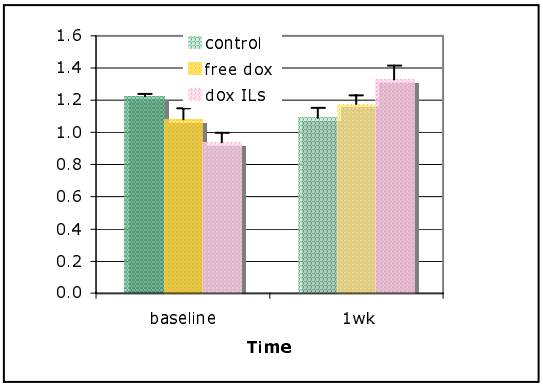

Figure 2. Tumor ADC values for three treatment groups

plateaued and the dox-IL group volume decreased compared to 1 week volumes. The mean tumor ADC values are shown in Figure 2, and reveal a trend of decreasing ADC in the control group, a slight increase in ADC for the free dox group and a larger increase in ADC for the dox-IL group. A correlation was found when the change in volume at 2 weeks was plotted vs. the change in ADC at 1 week for all tumors (R^2=0.82). No correlation was found for 1week volume change vs. 1 week ADC change.

Discussion: These preliminary results from our ongoing study demonstrate that the tumor growth inhibition from dox-ILs is greater than from a comparable dose of free doxorubicin, and that the changes in tumor volume may not be evident as early as changes in MR measured tumor ADC. The early increases in tumor ADC observed at 1 week post treatment appear to be correlated with tumor growth inhibition measured 2 weeks post-treatment. The increased anti-tumor efficacy of the dox-ILs is consistent with other studies and may be due to the fact that a higher amount of doxorubicin is delivered into tumor cells using the dox-ILs. The early ADC changes observed post-treatment support the use of diffusion-weighted MRI for evaluation of targeted therapies such as dox-ILs.

References: (1) Park JW, Clin Canc. Res. 2002;8:1172-1181. (2) Jennings D, Neoplasia, 2002; 4(3)255-62. (3) Park JW, J. Control. Release 2001;10:95-113.

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