Pharmacokinetics and Distribution of Anti-HER2 Targeted and Non-targeted Liposomes in a Breast Cancer Xenograft Model using MRI

L. J. Wilmes[1], K-L. Li[1], J. Gibbs[1], L. M. Fleming[1], D. Kirpotin[2], D. Drummond[2], J. W. Park[3], N. M. Hylton[1]

[1]Radiology, University of California San Francisco, San Francisco, CA, United States, [2]Hermes Biosciences, South San Francisco, CA, United States, [3]Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, United States

Background: Cancer therapies designed to target specific cell surface receptors that are over-expressed on tumor cells have the potential to increase the efficacy and selectivity of the treatment of breast and other cancers. For example, anti-HER2 doxorubicin immunoliposomes have been shown to have increased anti-tumor activity compared to other forms of doxorubicin [1]. The ability to non-invasively assess the distribution of targeted agents can aid in the development and assessment of new targeted therapeutics. Previous work has shown that uptake of gadolinium (Gd)-encapsulating anti-HER2 immunoliposomes (ILs) by HER2 over-expressing tumors can be detected by MRI [2]. The current work utilizes pharmacokinetic modeling to assess the behavior of antibody-targeted vs. non-targeted liposomes in a HER2-overexpressing model of human breast cancer.

Methods: GdDTPA-BMA encapsulating anti-HER2 targeted immunoliposomes (ILs) and non-targeted liposomes (NTLs) with a low permeability to water (IMP) were prepared (DSPC/DPPC/Chol/PEG-DPSE, mean diameter ~75nm). Immunoliposomes were targeted via an F5 scFv antibody fragment. Nude mice were implanted with the HER2/neu over-expressing human breast cancer line BT474. Tumor-bearing mice were imaged in pairs prior to, immediately after and up to 120 h post-i.v. injection with Gd-liposomes (0.05 mmol GdDTPA-BMA/kg). 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 high-resolution coronal 3DFGRE image was acquired at each time point (TR/TE 17/4.2ms, FOV 8 cm, matrix 512x256). T1 was measured using a 3D variable flip angle fast gradient echo technique. Signal intensity was calculated for regions of interest (ROIs) spanning the whole tumor volume and in blood. T1 was also calculated for tumor ROIs. Kinetic analysis was performed by fitting the early part (≤ 24 h) of the tissue signal intensity enhancement curve to a unidirectional two-compartment model [2]:

$$C(t) = k^{trans} \int_0^t C_p(t')dt' + fPV \cdot C_p(t)$$

The integral can be estimated as the area under the plasma tracer concentration curve, $C_p(t)$. The fPV was estimated as the ratio of the tissue and the plasma concentration at 5 minutes following injection of Gd-liposomes. Reported values were expressed as mean ± SE. Changes in vascular parameters were evaluated using a two-tailed Student's t-test, with a $p < 0.05$ was considered statistically significant.

Results: The group average of tumor tissue liposome uptake curves (IMP-NTLs, n=4, and IMP-ILs, n=4), expressed as the changes in tumor signal intensity vs. time, are shown in Figure 1. The change in blood SI was comparable for both IMP-ILs and IMP-NTLs, therefore an average plasma concentration curve was used for them. Kinetic analysis resulted in similar fractional plasma volume (fPV) for the two groups, but an apparently higher K^{trans} for the IMP-ILs than for the IMP-NTLs (0.007051± 0.00088 vs. 0.004821 ± 0.000163 min^{-1}, %differences = 46%, $p = 0.0469$). A good correlation was found between change in MRI tumor signal intensity and change in T1 values at 24 hr post-liposome injection (r^2=0.99917)

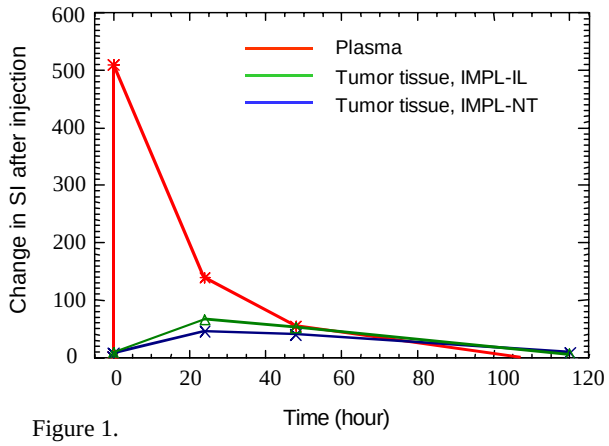

Figure 1.

Discussion: Because it has been previously demonstrated in studies using radiolabels that there is no difference in tumor accumulation between targeted and non-targeted liposomes, it is hypothesized that the higher apparent K^{trans} observed for targeted Gd-liposomes (IMP-ILs) does not reflect an increased vascular permeability to the IMP-ILs, but an increased average relaxivity due to the disruption of the liposomes upon cellular internalization. The correlation between the change in tumor SI and the change in tumor tumor T1 supports the use of SI values for this pharmacokinetic modeling.

References: (1) Park JW, Clin Canc. Res. 2002;8:1172-1181. (2) Wilmes LJ, Proc ISMRM, 2000; 250. (3) Tofts PS, J. Magn. Reson. Imaging 1999;10:223-232.

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