Monitoring Chemotherapy Induced Changes in the Carcinogen ENU Induced Infiltrating Ductal Adenocarcinoma and Non-Infiltrating Papillary Adenocarcinoma by Longitudinal MRI studies

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Purpose

It is well known that carcinogen ENU can induce benign and malignant tumors. In this study we utilized this wide variation of tumor types and tumor grades to simulate human breast cancer, and studied their response to chemotherapy (Taxotere). Longitudinal MRI was applied to measure the tumor volume and the contrast enhancement kinetics of a small extracellular agent Gd-DTPA-BMA and a medium size blood pool agent Gadomer-17. We investigated whether the vascular parameters measured by contrast enhanced MRI at an early time can differentiate responders from non-responders at later times, thus to predict therapy outcome.

Methods

53 Sprague-Dawley rats were injected with 90 mg/kg carcinogen ENU (N-ethyl-N-nitrosourea). Forty seven mammary tumors appeared within 9 months, and 35 tumors grew to 1.0 cm for the MRI study, which included 23 infiltrating ductal adenocarcinoma (IDC), 3 non-infiltrating papillary adenocarcinoma (NPC), 7 fibroadenoma (FA), 1 Sclerosing adenosis, and 1 papilloma. The baseline MRI was conducted when the tumor reached 1 cm. The imaging protocol included a T2-weighted sequence for volumetric measurement, and the dynamic study using a small molecular weight agent Gd-DTPA-BMA (®Omniscan, 0.1 mmol/kg), followed by an intermediate molecular weight agent Gadomer-17 (0.05 mmol/kg, provided by Schering AG, Germany). After the MRI study was completed the rats received i.v. injection of 4 mg/kg Taxotere. Three follow-up MRI studies were performed, once per week (noted as W1, W2, and W3). The rats continued to receive weekly Taxotere treatment after each MRI study. The volume of each tumor was measured, and depending on the volumes at W3 compared to the baseline, the tumors were separated into responders (volume decreased by 50%), non-responders (volume increased by 50%), and stabilizer (others). Also, the response at each time point compared to the baseline was analyzed. The MRI enhancement parameters (at 30 sec, 1-min, and 2-min) and the K21 decay rate were used to investigate whether any of these parameters themselves, or the changes compared to the previous time measures, can be used to differentiate responders from non-responders at a later time.

Results

Among these 35 tumors, 29 tumors (20 IDC, 3 NPC, 4 FA, 1 adenosis, and 1 papilloma) have completed the longitudinal study at 4 time points. According to the tumor volume at the end of week-3 compared to the baseline (noted as GR), the tumor was classified into responder (GR < 0.5), stabilizer (0.5 < GR <1.5), and non-responder (GR > 1.5). Of the 20 IDC, 9 were responders, 5 were stabilizers, and 6 were non-responders. Interestingly all 3 NPC were stabilizer. Three fibroadenomas were non-responders and only one FA was a responder. Figure 1 shows the T2-weighted images and the contrast enhancement kinetics from an IDC which showed a consistent regression. Figure 2 shows another IDC which grew larger over time. However, not every tumor was responding consistently. Given the complicated response pattern, the statistical analysis was only performed for IDC and the response at each time point was analyzed separately. Tumor size at week-1 compared to the baseline was calculated, and separated into +/- growth groups. Among all 8 MRI parameters, the baseline Gadomer-17 enhancements at 1-min and 2-min at baseline showed a significant difference ($p < 0.05$, Wilcoxon rank-sum tests) between the 2 groups with +/- growth at week-1. The same analysis was applied at week-2 and week-3, but no MRI parameters revealed a significant difference between different growth groups at week-2 and week-3.

One responder (infiltrating ductal adenocarcinoma)

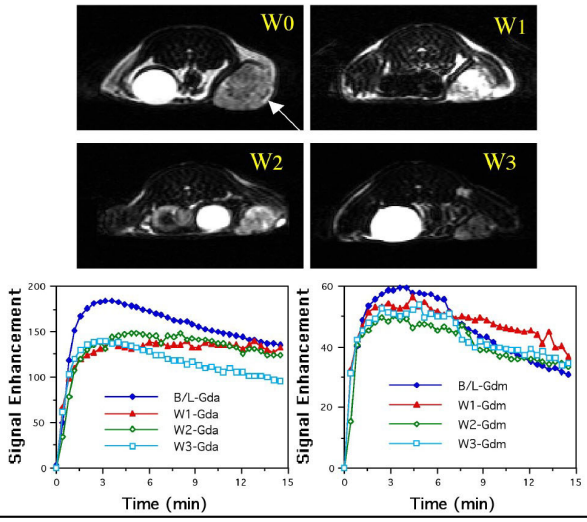

Figure 1: The T2-weighted image, and the enhancement kinetics measured by Gd-DTPA-BMA(left) and Gadomer-17(right) in one responder tumor (infiltrating ductal adenocarcinoma). The tumor showed continuous regression over time. The kinetics measured by Gd-DTPA-BMA showed reduced intensity after the first treatment, and the pattern of the curve became more flattened (i.e. no wash-out).

One non-responder (infiltrating ductal adenocarcinoma)

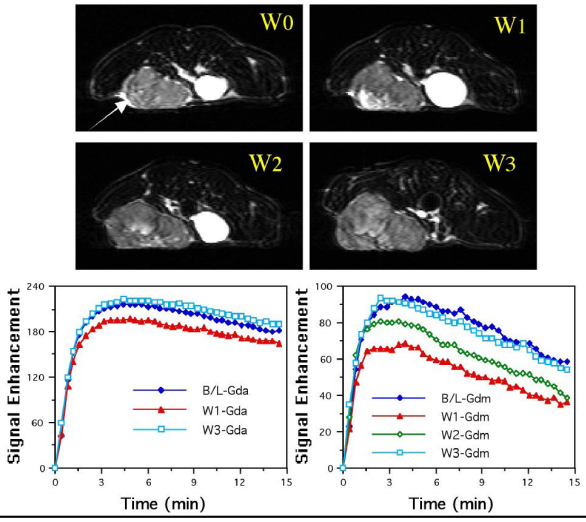

Figure 2: The T2-weighted image, and the enhancement kinetics measured by Gd-DTPA-BMA(L) and Gadomer-17(R) in one non-responder tumor (infiltrating ductal adenocarcinoma). Apparently the tumor grew larger and larger over time. The Gd-DTPA-BMA kinetics were similar over time, and Gadomer-17 kinetics showed a great reduction at week-1 then recovered to the baseline level at week-3.

Discussion

The volumetric changes and contrast enhancement changes in ENU induced tumors receiving Taxotere were measured by longitudinal MRI. ENU induced benign and malignant tumors (came with 2 major types, infiltrating ductal adenocarcinoma, and non-infiltrating papillary adenocarcinoma simulating in-situ cancers). Among all tests, only the baseline Gadomer-17 enhancements at 1-min and 2-min revealed a significant difference between IDC's which grew bigger at week-1 versus those which shrank at week-1. This maybe interpreted as that tumors with a higher vascularity measured by Gadomer-17 had a better response (shrinkage), possibly due to more drug delivery. The data also indicated that although ENU induced tumors came with a large variation, they also showed different responses to therapy. Although ENU induced tumors may simulate the variety in human breast cancer, but it may not be a good tumor model for drug response testing.

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