

Preliminary evidence of a vascular normalization biomarker in trastuzumab-treated HER2+ breast cancer

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Purpose

The primary goal of this study is to identify and validate quantitative biomarkers to differentiate responsive vs. resistant tumors to targeted treatment with a goal to optimize therapy on an individual basis. We report longitudinal DCE-MRI studies designed to identify early changes in pharmacokinetic parameters obtained from trastuzumab-sensitive and resistant mouse models of HER2+ breast cancer.

Methods

Nude athymic female mice ($N = 25$) were subcutaneously implanted with 10^7 BT474 cells, trastuzumab-sensitive breast cancer cells, or HR6, trastuzumab-resistant breast cancer cells.¹ Tumors grew to an average volume of 250 mm^3 and were randomly assorted into four groups: BT474 treated, BT474 control, HR6 treated, and HR6 control. Treated groups received trastuzumab (10 mg/kg) on baseline and day 3, while controls received comparable saline injections. Animals were sacrificed on day 4 and tumors resected for CD31 immunohistochemistry (IHC) analysis. DCE-MRI (7.0 T Agilent) was conducted at baseline, day 1, and day 4. Dynamic T_1 -weighted images were acquired using a spoiled gradient echo sequence at a temporal resolution of 12.8 seconds for 20 minutes with the following parameters: TR/TE = 100/2.1 ms, $\alpha = 25^\circ$, NEX = 2, acquisition matrix = 64×64 , FOV = $28 \times 28 \text{ mm}^2$, and 15 (1 mm) slices. Baseline images were acquired, then a bolus of Gd-DTPA (0.05 mmol/kg) was administered. A voxel-based DCE-MRI analysis, employing the standard Tofts model and a population AIF², was performed to return parametric maps of K^{trans} and v_e .

Results

Figure 1 presents (A) representative K^{trans} maps and (B) the corresponding changes in treated BT474 and HR6 tumors from baseline to day 4. Treated BT474 tumors presented a significant increase in K^{trans} on day 1 and day 4 compared to HR6 treated tumors ($P < 0.05$, $P < 0.01$, respectively); also noted was an increase compared to BT474 saline control tumors on day 4 ($P < 0.05$). This was revealed prior to changes in tumor size (not shown, $P = 0.29$), therefore indicating a potential early biomarker of response. Histological analysis (day 4) also showed a significant increase in CD31 microvessel density ($P = 0.03$) on BT474 treated tumors. Comparison of the treated and control nonresponder HR6 groups revealed no significant differences (day 1 or day 4) in the imaging or histological analysis ($P > 0.05$).

Discussion

It has been previously established that trastuzumab has a significant effect on HER2+ breast cancers.³ However, this response is only effective in an estimated 25-50% of HER2+ patients, and is generally demonstrated by change in tumor size after weeks of therapy.^{3,4} This preliminary study suggests that the DCE-MRI parameter, K^{trans} , may serve as an early biomarker of response in trastuzumab sensitive HER2+ tumors, detecting intratumoral changes before changes in tumor size. An increase in the parameter, K^{trans} , parallels results revealed by IHC through an increase in CD31 microvessel density staining in the BT474 treated group. These results display potential significant clinical impact for measuring whether a tumor is resistant or sensitive to trastuzumab, early in the course of therapy. K^{trans} signifies an increase in permeability and/or perfusion characteristics; we therefore hypothesize that we are observing an improvement in drug delivery through vessel normalization. Trastuzumab-induced vessel normalization has been previously noted⁵, however these results have not been translated clinically. The preclinical data presented here, though preliminary, indicates that there may be an optimal timing window for concomitant cytostatic therapies.

Conclusion

This work demonstrates that the clinically translatable DCE-MRI parameter, K^{trans} , has the sensitivity to differentiate between trastuzumab-resistant and sensitive HER2+ tumors just one day after an initial dose of therapy. This increase in K^{trans} suggests properties of vessel normalization and potential improvement in intratumoral drug delivery. Therefore, we are continuing investigation of K^{trans} as a biomarker for vessel normalization.

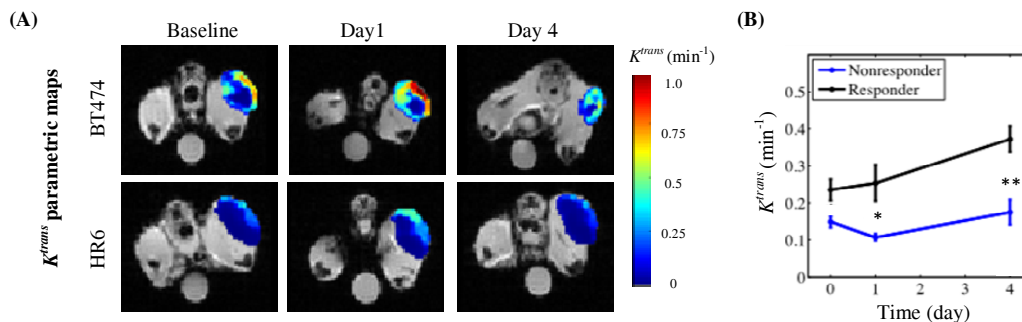


Figure 1. An increasing K^{trans} is (A) visualized in the trastuzumab treated BT474 tumors (responders) compared to treated HR6 tumors (nonresponders) and (B) presented with corresponding K^{trans} values.

References

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