MRI Measurements of Tumor Size and Pharmacokinetic Parameters as Early Predictor Variables in Breast Cancer Patients Undergoing Neoadjuvant AC-Chemotherapy

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Introduction

Neoadjuvant chemotherapy plays a major role in patients with locally advanced breast cancer for down-staging tumors to render them operable. It has also been increasingly used in readily operable early stage cancer to facilitate breast conservation surgery. If the response of tumor can be determined or even predicted at early times after the chemotherapy is initiated, the patient could be spared from ineffective treatment and the associated morbidity. This study investigates the value of tumor size changes or enhancement pharmacokinetic changes obtained during early stage of AC chemo-regimen (after 1 or 2 cycles of AC) as predictors of final outcome after completing 4 cycles of AC. The analyzed MRI parameters include tumor size measured using 1D-RECIST, 2D-WHO, and 3D-volume criteria, as well as two widely used pharmacokinetic parameters, K^{trans} and k_{ep} [1].

Methods

Twenty-seven patients with confirmed breast cancer (31-75 yrs., median 48) were included in this study. The 1-D tumor size prior to chemo-regimen ranged from 1.5 to 9 cm. The patients were imaged on a 1.5T Phillips Eclipse MR scanner using a dedicated bilateral breast coil. The MRI protocol included a localizer scan, sagittal view T1-weighted pre-contrast scan for the breast of concern (TR/TE=1000/12 ms, FOV=20 cm, 256x256-matrix and 3-3.5 mm thickness) and dynamic contrast-enhanced sequence (DCE-MRI). The DCE-MRI is based on a 3D gradient echo pulse sequence with TR/TE=10/3.6 ms, flip-angle= 20^o, 32 bilateral-axial partitions with 4-mm thickness, FOV=32-38 cm, and acquisition-matrix=256x128. Sixteen frames (repetitions) were prescribed, each of which was acquired in 42 sec. The contrast agent (Omniscan®, 1 cc/10 lbs) was injected at start of the 5^{th} frame acquisition, and then followed by a saline flush. All patients received a baseline MRI prior to start of their chemo-regimen and at least 2 additional F/U MRI scans during the course of treatment. The regimen consisted of 2-4 cycles of dose-dense AC (Adrimycin and Cyclophosphamide) followed by Taxane regimen (TCa±H, Taxane and Carboplatin with Herceptin for Her-2/neu positive patients). Twenty patients out of 27 received 4 cycles of AC before being switched to Taxane regimen or having a surgery. The remaining 7 patients only received 2 cycles of AC, and were switched to Taxane regimen earlier due to lack of response based on clinical exam or other imaging findings. The 20 patients who completed 4 cycles AC were separated into 2 groups based on the RECIST criteria [2] in the F/U MRI study after 4 AC. The responder was defined as those showing greater than 30% 1-D reduction. The non-responders included those showing less than 30% 1-D reduction and the 7 patients receiving only 2 cycles of AC. All together there were 16 responders and 11 non-responders. For each group the changes in the tumor size and the pharmacokineitc parameters measured at the early F/U study were compared to their respective baseline MRI measurements, and then the changes in these 2 groups were compared to each other. The pharmacokinetic parameters (K^{trans} and k_{ep}) were calculated based on both ROI-averaged and pixel-by-pixel analyses. The changes of K^{trans} and k_{ep} measured from the ROI analysis, and the 90%, 80%, 70%, and the median (50%) K^{trans} and k_{ep} measured from the pixel-by-pixel analysis were investigated, and the significance level was tested using 2-tail paired t-test ($P < 0.05$).

Results

The classification of responders and non-responders based on the RECIST after 4 cycles AC was consistent with the equivalent classifications set by WHO (minimum bidimensional reduction of 50% for responder) [2] and by volume (reduction of 65% or more for responder) [2] for those 20 patients who received 4 cycles of AC. The prediction of response based on 3 size criteria in the early F/U after 1-2 cycles AC was investigated. The early size changes mis-predicted 2 patients in the responder group as non-responders based on RECIST (+4% and -7%, respectively, w/ cut-off @-15%). The same 2 patients were also mis-predicted by WHO (-7% and -25%, respectively, w/ cut-off @-27%) and volumetric (-29% and -14%, respectively, w/ cut-off @-38%) criteria. One other patient in the responder group was mis-predicted by WHO (-25%) and volumetric (-36%) criteria, but not by RECIST (-21%) at the early F/U. One patient in the non-responder group (n=11) was mis-predicted as a responder by WHO criteria (-29%). For responder group, significant reductions in both K^{trans} and k_{ep} were observed at the early F/U with respect to the baseline in both ROI-averaged and pixel-by-pixel analyses [3], whereas no statistically significant change was observed for either parameter in the non-responder group. The changes are summarized in the table.

	Responder (n=16)	**Non-responder (n=11)**
ROI-Ave. ΔK^{trans}	-18±24 (%) ($P < 0.01$)	3±22 (%)*
90% population ΔK^{trans}	-20±28 (%) ($P < 0.05$)	7±29 (%)*
80% population ΔK^{trans}	-21±29 (%) ($P < 0.05$)	6±24 (%)*
70% population ΔK^{trans}	-21±29 (%) ($P < 0.05$)	6±21 (%)*
50% population ΔK^{trans}	-21±27 (%) ($P < 0.01$)	6±19 (%)*
ROI-Ave. Δk_{ep}	-20±19 (%) ($P < 0.001$)	1±10 (%)*
90% population Δk_{ep}	-26±20 (%) ($P<0.0005$)	1±15 (%)*
80% population Δk_{ep}	-25±21 (%) ($P<0.0005$)	1±13 (%)*
70% population Δk_{ep}	-24±22 (%) ($P < 0.001$)	1±13 (%)*
50% population Δk_{ep}	-21±24 (%) ($P < 0.005$)	1±11 (%)*

Table: The changes (±standard-deviation) observed at the early F/U in K^{trans} and k_{ep} with respect to that of the baseline for responder and non-responder groups. Both parameters were calculated by fitting the ROI-averaged time course data as well as pixel-by-pixel data. (*: statistically non-significant)

Discussion

Our study shows that the tumor size change as measured at the early F/U MRI (1-2 cycles of AC) represents a reasonably good predictive value on how the tumor would respond after 4 cycles of AC. Excluding those 7 patients who were switched to Taxane regimen only after 2 cycles of AC, size-change based on RECIST correctly predicted 18 out of 20 patients. These two patients had septal and diffuse enhancement phenotypes [4]; both made defining the border difficult. All 3 size criteria mis-classified them. All K^{trans} and k_{ep} pharmacokinetic parameters obtained using ROI or pixel-by-pixel analyses presented in this study showed significant reduction in the responder group but not in non-responder group, thus suggesting their potential as early response predictors. Those 2 patients who were mis-predicted as non-responders based on early size change showed reductions in both K^{trans} and k_{ep} in the early F/U study (32-37% ΔK^{tran}, 24-29% Δk_{ep} for one patient and 25-31% ΔK^{tran}, 12-18% Δk_{ep} for the other). These percentage reductions were comparable to the changes in the responder group in the table above. MRI measurement of changes in tumor size and pharmacokinetic parameters may serve as early response predictors for patients undergoing neoadjuvant chemotherapy.

Ref.: [1] Tofts P. JMRI 7:91-101, 1997. [2] James et al. JNCI 91:523-528, 1999. [3] Yu et al. Rad. Res. 158:152-158, 2002. [4] Esserman et al. ASO 8:549-559, 2001.

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