MRI Monitoring of Neoadjuvant Chemotherapy Response in Breast Cancer Using an Aggressive Treatment Protocol: Doxorubicin-Cyclophosphamide Followed by Taxane + Carboplatin ± Trastuzumab/ Bevacizumab Regimen

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Purpose:

Neoadjuvant chemotherapy has become more widely used in management of breast cancer. Not only that it can downstage inoperable locally advanced disease to render tumor operable, it can also be used to downstage readily operable tumors to facilitate breast conservation surgery. It has been shown to improve both relapse-free and overall survival in patients with locally advanced breast cancer. Neoadjuvant chemotherapy can also be used to test the response of each individual's cancer to a specific drug regimen in vivo, which may provide very useful information for initial drug testing or for future management of recurrence. Recently it was reported that a pathological complete response (pCR) is a surrogate of improved survival [Amat et al. Breast Cancer Res Treat. 2005; 94:255-263]. Given these benefits, our institution is actively enrolling patients into the neoadjuvant chemotherapy protocol. In addition to patients with locally advanced disease, those with clinically documented lymph node involvement, regardless of their primary tumor stage, were also enrolled. The protocol included the anthracycling-based regimen (AC, first line) and Taxane-based regimen (second line, with Carboplatin and Trastuzumab for Her-2/neu positive cancer). Longitudinal MRI was performed to monitor the response to each regimen. Patients received a baseline MRI, then several follow-ups during the course of treatment, then a final MRI before surgery. The goal is to design an optimal treatment protocol, adjusted based on the response pattern, to achieve the highest pCR rate. Collectively we would like to address these questions: 1) what are overall pCR rate in Her2 +/- cohorts? 2) whether response to the first line AC regimen affects the final pCR? 3) when is a good time to determine the early AC response? 4) what are the sensitivity, specificity, and accuracy of MRI in predicting residual disease? 5) does tumor morphology affect the final outcome or impact on surgical decision?

Methods:

48 subjects (29-75 yo, median 48) from July 2003 to April 2006 were included in this study. The tumor size ranged from 0.9 cm to 8.5 cm (median 2.4 cm). All patients received 2-4 cycles bi-weekly AC (doxorubicin and cyclophosphamide) with growth factor support, followed by Taxane regimen (TCa ± H), including paclitaxel or Nab-paclitaxel (Abraxane) and Carboplatin, with Trastuzumab (Herceptin) for Her-2 positive patients, then surgery. Five Her-2 negative patients also received bevacizumab (Avastin) with taxane. The Taxane regimen consisted 3-4 cycles, each cycle with 3-weeks on and 1-week off Taxane and Carboplatin, and weekly Herceptin. MRI protocol included a T1-weighted pre-contrast Sagittal view scan from the concerned breast, and an axial view dynamic contrast enhanced scan using a 3D SPGR (RF-FAST) pulse sequence. Thirty-two axial slices with 4 mm thickness were used to cover both breasts. The subtraction images at 1-min after injection was used to determine the MRI phenotype and the size of the lesion (the index lesion in case of multi-nodular pattern). The long and short dimensions were measured on the MIPs (maximum intensity projections) of the subtraction images. The response was assessed based on the two dimensional area on MIPs, then converted to % 1-D size reduction. When the 1-D size reduction was greater than 10% after 1 cycle AC, 20% after 2 AC, or 30% after 4 cycles it was determined as a AC responder, otherwise a non-responder. Fig. 1 shows two examples, both were NR after 1 cycle AC but turned out to have different outcome. After taxane when the tumor has shrunk to barely differentiable, as long as a noticeable enhancement from the previous cancer site which was higher than that of normal tissues, it is considered as residual disease. Based on the 3D morphological pattern of the lesion, they were classified into three MRI phenotypes: I- solitary mass; II- multi-nodular pattern (separately differentiable masses); III- diffuse pattern (a regional enhancement without well-defined border).

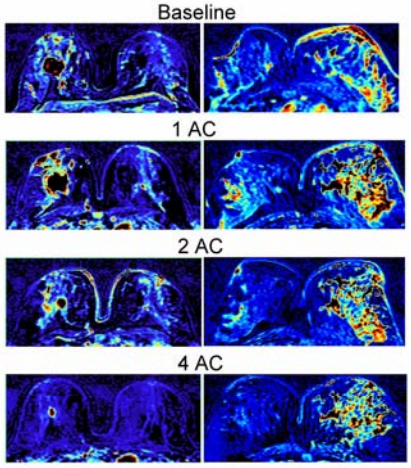

Fig.1 Two patients both received F/U MRI after 1, 2, and 4 cycles AC. The left patient was Her2 negative, NR after 1AC, then started to show response. The right patient was Her2 +, NR in all 3 F/U studies.

Results:

All patients received surgery after the last MRI. The specimen was cut every 5 mm for pathological examination, and the extent of residual disease was reported as: 1) with invasive cancer- a solid mass or scattered cells within a region, 2) no invasive cells but with DCIS, and 3) no evidence of tumors. Using the MD Anderson criteria pCR was defined as no invasive tumor, therefore includes 2)+3). Table 1 summarizes the pCR rate in Her2 +/– cohorts, separated by AC response as AC-R vs. AC-NR. Her2 + cancers receiving Herceptin had a significantly higher pCR rate (78%) compared to Her2 – cancers (36%, p = 0.015 **). In Her2 –, AC-NR group, not a single case achieved pCR (0/8, 0%), which was lower than that in AC-R group (9/17, 53%, p = 0.007 *).

Table 1: The pCR rate and MR diagnosis of residual cancer in Her2 +/-, AC R/NR Groups

	Her2 Negative (N=25)		Her2 Positive (N=23)	
Overall pCR	**9/25 (36%)**		**18/23 (78%) ****	
	AC-NR (N=8)	AC-R (N=17)	AC-NR (N=12)	AC-R (N=11)
Group pCR	**0/8 (0%)**	**9/17 (53%) ***	9/12 (75%)	9/11 (82%)
MR Sensitivity	5/8	4/8	3/3	1/2
MR Specificity	0/0	7/9	8/9	9/9
MR Positive PV	5/5	4/6	3/4	1/1
MR Negative PV	0/3	7/11	8/8	9/10
MR Accuracy	5/8 (63%)	11/17 (65%)	11/12 (92%)	10/11 (91%)

Interestingly in Her2 + cancers AC-NR and AC-R had a similar pCR rate (9/12, 75% vs. 9/11, 82%), i.e. not affected by AC response. There were 13 AC responders who had both F/U MRI after 1 cycle and 4 cycles AC, and of them 4 were determined as NR after 1 cycle AC. That is, the response evaluated after 1 cycle AC may be too early, and mis-predict the final AC response in 4/13 (31%) cases. The sensitivity, specificity, positive predicted value, negative predicted value, and accuracy of MRI in diagnosis of residual disease are summarized in Table 1. The accuracy in Her2 – group (16/25, 64%) is significantly lower than that in the Her2 + group (21/23, 91%, p = 0.04). The reason was attributed to 7 false negative cases in this group. When the residual disease was presented as scattered cancer cells or invasive foci smaller than 3 mm, no residual enhancements were detected, thus it was very difficult for MRI to correctly diagnose them. Lastly we also investigated whether the lesion phenotype was associated with pCR or type of surgery. The lesions were categorized into solitary mass (e.g. Fig.1 left), multiple nodules, and diffuse pattern (Fig.1 right). In each type, some achieved pCR, some not; thus the phenotype was not associated with final treatment outcome, nor the type of surgery.

Discussion:

In this study we performed longitudinal MRI to follow patients' response to an aggressive neoadjuvant chemotherapy protocol: 2-4 cycles AC followed by taxane+carboplatin, with Herceptin for Her2 + cancer. To address the 5 proposed questions: 1) The overall pCR rate was 36% for Her2 –, and 78% for Her2 + patients, which was much higher compared to published results using the standard therapy (4 cycles AC followed by taxane). MRI monitoring is very helpful to help determine an optimal protocol: 2) AC response may affect the pCR in Her2 – cohorts (AC responders are more likely to achieve pCR), but not in Her2 + patients. 3) The early response evaluated after 1 cycle AC may be too early; the first F/U after 2 AC is recommended. 4) MRI can predict pCR with 91% accuracy in Her2 + group, but it had a high false negative rate in Her2 – patients, failing to predict residual disease when it is presented as scattered cells or small foci. 5) There was no clear association between lesion phenotype with pCR or type of surgery.

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