MRI Monitoring of Neoadjuvant Chemotherapy Response in Breast Cancer of Different Phenotypes to Doxorubicin-Cyclophosphamide followed by Taxane + Carboplatin ± Trastuzumab Regimen

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Purpose

Neoadjuvant chemotherapy has become more widely used in the management of breast cancer. Not only that it can downstage the disease for breast conservation surgery, the response of each individual's cancer to each specific drug regimen can be tested in vivo, which may provide very useful information in case of recurrence. Furthermore, it has been shown that a pathological complete response (pCR) is a surrogate of improved survival. At our institution neoadjuvant chemotherapy was offered to patients with inoperable locally advanced disease, with clinically documented lymph node involvement, or to down-stage disease for breast conservation surgery or for a better surgical outcome. Patients received a baseline MRI before treatment, then several follow-ups during the course of treatment, then a final MRI before surgery. We investigated whether the MRI phenotype is associated with response in AC followed by Carbo-Taxel ± Herceptin regimen. The MRI morphological patterns in different treatment and response groups were compared. The residual cancer detected on MRI was correlated with pathological findings. Lastly the relationship between the response to AC and to TCa ± H was investigated, and the benefit of Herceptin in Her2/neu positive cancer was determined.

Methods

53 subjects (29-75 yo, median 48) from May 2003 to Oct 2005 were included in this study. The tumor size ranged from 0.9 cm to 8.5 cm (median 2.4 cm). Several earlier patients received AC (doxorubicin and cyclophosphamide) then surgery, and all others received AC followed by Taxane regimen (TCa ± H, Taxel and Carboplatin, with Herceptin for Her-2/neu positive patients), then surgery. Dose-dense AC treatment was given every 2 weeks, with growth factor support, unless intolerable. The Taxane regimen consisted 3 cycles, each cycle with 3-weeks on and 1-week off Taxel and Carboplatin, and weekly Herceptin. MRI protocol included a T1-weighted pre-contrast Sagittal scan from the concerned breast, and an axial bilateral 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 were used to determine the MRI phonotype 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 (Figure 1). Based on the 3D morphological pattern of the lesion, they were classified into four MRI phenotypes modified from Esserman et al. [Ann Surg Oncol. 2001 8(6):549-559], I- circumscribed mass, which has one primary mass with well-defined border; II- nodular pattern, which has multiple differentiable nodules; III- diffuse pattern, which demonstrates a regional enhancement without well-defined border, and IV- septal pattern, which involves almost the entire breast, as illustrated in Figure 1. The response was assessed based on the two dimensional area on MIPs, then converted to % 1-D size reduction. Depending on the final size determined in the last MRI compared to the size shown in baseline MRI, those showing less than 30% reduction was defined as non-responders (NR), greater than 30% and less than 100% as partial responders (PR), and those without detectable residual enhancements as complete responders (CR).

Results

Thirty-four patients had surgery within 2 months after the last MRI. Among them, 13 cases which were determined to have residual disease on MRI were found to have residual invasive cancer in pathological examination. In the remaining 21, MRI did not detect substantial enhancements. Of these, invasive cancers were found in 3 cases (with 3mm ILC, 1.5mm IDC, and islands of infiltrating IDC), and DCIS was found in 7 cases. Residual DCIS is still considered as pathological complete response (pCR). MRI-determined response to AC regimen is summarized in Table 1. The responses in groups with different MRI phenotype were not statistically different (68%, 79%, 50%, 67% for types I-IV, respectively). When a patient was determined not to show a good response to AC, the regimen was switched to Taxane after 2 cycles AC. Forty-nine patients completed 4 cycles AC, or AC followed by 3 cycles TCa± H, and the results are summarized in Table 2. No CR was found in the AC group, 13/23 (57%) in the AC+TCa group achieved CR, and 12/13 in the AC+TCaH achieved CR (In fact, the only NR in this group was a patient with Her2/neu negative primary cancer but Her2/neu + node). Of the 12 CR in AC+TCaH group, 4 were non-responder to AC, but they still achieved CR after TCaH. The rates of CR to these 3 treatment regimens were significantly different. In contrast, different MRI phenotype was not associated with response, thus not a good predictor of response.

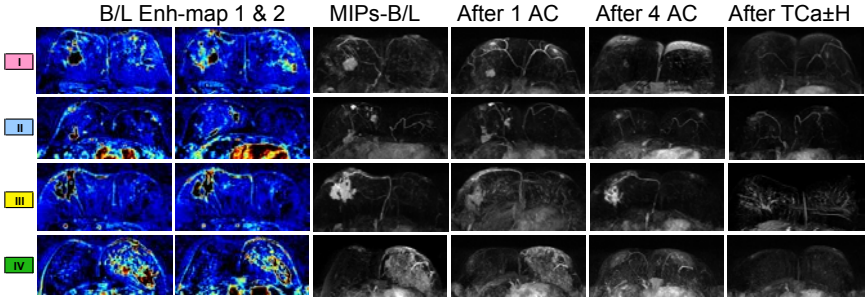

Table 1: The response to AC, with MRI phenotype coded by color

AC Treatment	Responder				Non-Responder			
All cycles (N=50)	17	11	4	2	8	3	4	1

I circumscribed mass
II nodular pattern
III diffuse pattern
IV septal pattern

Table 2: The response to three regimens, with MRI phenotype coded by color

Tatol N=49	CR				PR				NR		
AC only (N=13)					2	5	4			1	1
AC +TCa (N=23)	9	2	1	1	5	2	1	1		1	
AC + TCaH (N=13)	6	4	1	1					1		

Figure 1: Four cases illustrating 4 different MRI phenotypes. Color-coded enhancement maps from 2 slices in the baseline study are shown. The maximum intensity projections in the baseline study before chemo, after 1 cycle AC, after 4 cycles AC, and after completing all chemotherapy are also shown. All 4 cases showed a final complete response on MRI.

Discussion

MRI is known to be accurate in detecting residual cancer size in down-staging AC regimen. However, as a more aggressive protocol is used, the complete response rate becomes higher. In this study we showed that MRI is still performing well in predicting the extent of residual disease. However, in our setting we could not detect invasive cancer smaller than 3 mm, or the residual cancer which was presented as islands of malignant cells. Also, MRI could not detect residual DCIS (but still considered as pCR). The responses to the three different treatment regimens were significantly different, CR was found in 0/13 in AC groups, 13/23 in Her2/neu negative cancer receiving AC+TCa, and 12/12 in Her2/neu positive cancer receiving AC+TCaH. Exposure to AC treatment is considered necessary to optimize response, and our results showed that AC can be reduced to 2 cycles still to achieve CR. Positive Her2/neu is used to be an unfavorable prognostic factor, however, this maybe no longer true with the availability of targeted therapy Herceptin. However, it remains to be determined whether the pCR in this group is indeed translating to an improved survival.

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