MRI Monitoring of Neoadjuvant Chemotherapy in Breast Cancer: Association of MRI Morphological Patterns with Early and Final Responses in AC followed by Taxane ± Carboplatin ± Trastuzumab Regimen

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Purpose

It has been shown that different MRI phenotype in breast cancer may show different response to neoadjuvant chemotherapy with AC regimen [1-2]. In this study we investigated whether the morphological pattern is associated with response in dose-dense AC regimen, and in AC followed by Carbo-Taxel ± Herceptin (for positive or negative Her-2/neu). At our institution neoadjuvant chemotherapy was offered mainly due to three reasons: 1) with locally advanced disease which was inoperable, 2) with clinically documented lymph node involvement, 3) down-staging 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. The MRI morphological patterns in different treatment groups and response categories were compared. Whether the early response after 1-2 cycles AC is predictive of final response after 4 cycles AC was investigated. Lastly the relationship between the response to AC and to TCa ± H was investigated, and the benefit with addition of Herceptin was also determined.

Methods

23 subjects (32-75 yo, median 47) were included in this study. The first several patients received 4 cycles AC (doxorubicin and cyclophosphamide) then surgery. Later patients received a more aggressive protocol with AC followed by Taxane regimen (TCa ± H, Taxane and Carboplatin, with Herceptin for Her-2/neu positive patients), then surgery. Dose-dense treatment was given every 2 weeks, with growth factor support, unless intolerable. MRI protocol included a T1-weighted pre-contrast Sagittal view scan from the concerned breast, and an axial view dynamic contrast enhanced SPGR 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 generate MIPs (maximum intensity projections), and from which the long and short dimensions were measured. Based on the 3D morphological pattern of the lesion, they were classified into four types according to Esserman et al. [1], I- circumscribed mass, which has one primary mass with well-defined border; II- nodular pattern, which is consisted of connecting nodules without well-defined borders; III- diffuse pattern, which demonstrates a regional enhancement without differentiable mass or nodule, and IV- septal pattern, which involves almost the entire breast. Figure 1 shows the MIPs of three types, in baseline, after 1 cycle AC, and after 4 cycles AC studies. In these cases, type I had the best response, type II showed a partial response, and type IV had a minimal response.

The response was assessed based on the longest dimension on MIPs, as shown in Figure 1. If there are multiple differentiable lesions in type I or type II, one index lesion (the largest or the most well-defined) was chosen. 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). Those who did not have detectable disease as complete responders (CR). In cases which the surgery occurred within 1 month after the last MRI, size determined on MRI was compared to the pathological size. The morphological patterns in different treatment groups and response categories were compared.

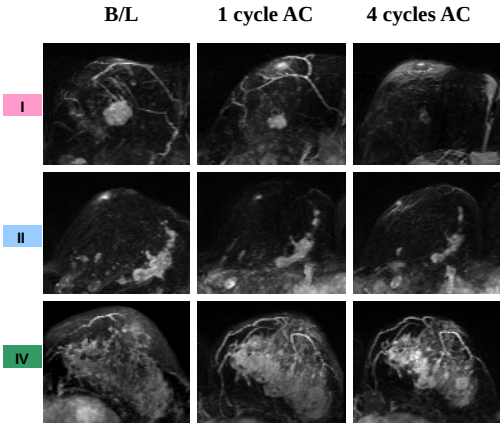

Figure 1: The maximum intensity projection view of three types of cancer, type I-circumscribed mass, type-II nodular pattern, and type IV-septal pattern, in the baseline, after 1-cycle AC, and after 4-cycles AC studies.

Table 1: The number of patients in each group, separated into different morphological categories indicated by colors.

Tatol N=23	CR	PR	NR
AC only (N=7)		3 3	1
AC + TCa (N=7)	1 1	2 1 2	
TCa only (N=1)		1	
AC + TCaH (N=7)	3 2 1		1*
TCaH only (N=1)	1		

* A unenhanced hypointense lesion in last MRI before surgery
The tumor was not well enhanced at B/L, and Her-2 negative

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

Table 2: The responders and non-responders to AC treatment, assessed after 1-2 cycles and after 4 cycles

AC Treatment	Responder	Non-Responder
1-2 cycles (N=18)	6 5	4 1 1 1
4 cycles (N=14)	6 5	2 1

Responder is >15% after 1-2 cycles, >30% after 4 cycles

Results

Sixteen patients had surgery within 1 month after the last MRI. Among them 7 were complete pathological responders, and MRI did not detect any residual enhancements from previous cancer site. The Pearson's regression analysis showed a significant correlation between MRI and pathological size ($r = 0.89$, $p < .01$). The MRI-determined response is summarized in Table 1. 6/7 patient received AC only were PR, patients received Carbo-Taxane were responders 2/8 CR and 6/8 PR, and most patients who received Carbo-Taxane with Herceptin were complete responders (7/8). Among these 7, 6 were complete pathological responders and one had a 3 mm residual cancer. The morphological pattern was not correlated with response, as indicated in Table 1 by different color blocks. For example, of the 6 PR in AC only group, 3 were type-I and 3 were type-II. Of 7 CR in AC+TCaH group, 3 were type-I, 2 were type-II, and 1 was type-IV. In almost every response group both type-I and type-II were seen. Table 2 summarizes the response to AC treatment, assessed after 1-2 cycles AC and after 4 cycles AC. Of all 18 patients who had an F/U after 1-2 cycles AC, 11 were responder and 7 were non-responders. Again the morphologic pattern was not different. All patients who showed an early response (>15% reduction) were responders after 4 cycles AC (47% to 86% reduction). For those who did not show early respond to AC, they all responded to the following Carbo-Taxane regimen (except the NR* in table 1). There was no association between response to AC and response to TCa ± H. Two patients who did not respond to AC still achieved a complete pathological response after TCaH. In Her-2/neu negative patients, 4 who did not respond to AC achieved partial response after TCa, and the other 2 who responded to AC achieved a complete pathological response. Lastly, patients who received Herceptin (AC + TCaH) had a better response than those who received AC + TCa without Herceptin. All 7 Her-2/neu positive patients achieved a complete response. Of 8 Her-2/neu negative patients who did not receive Herceptin, only 2 were complete responders.

Discussion

The findings were: 1) The size determined on MRI was highly correlated with final pathological size. No enhancement from previous cancer site predicted a complete pathological response, except one case with 3mm residual cancer and the NR* in AC + TCaH group. In this case MRI showed a hypointense lesion without strong enhancement in the baseline, and still showed a hypointense lesion but not enhanced in the last study. This lesion was Her-2/neu negative, but with Her-2/neu positive nodes. 2) The MRI morphological pattern type-I and II (circumscribed mass or nodular pattern) did not show different responses to the dose-dense AC regimen, or AC followed by TCa ± H regimen. 3) The early response after 1-2 cycles AC predicts the response after 4 cycles AC. 4) The response to AC was not associated with response to TCa + H, but might enhance the response to TCa without H. 5) The addition of Herceptin in Her-2/neu positive patients enhanced the treatment outcome.

References [1] Esserman et al. Ann Surg Oncol. 2001 8(6):549-559. [2] Partridge el al. Am J Roentgenol. 2002 179(5):1193-1199.

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