Quantitative MR Spectroscopy to Monitor Treatment Response of Breast Cancer to Neoadjuvant Chemotherapy

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Introduction

In vivo proton MR spectroscopy (^{1}H-MRS) has been proven helpful for the detection and therapy response monitoring of breast cancer based on choline-containing compounds (Cho). Bolan et al [1] suggested that quantification of Cho levels using an internal reference method is valuable for measuring tumor response to treatment regimens. Meisamy et al [2] found that change in Cho levels could provide an indicator for predicting clinical response as soon as 24 hours after the first dose of doxorubicin-based chemotherapy. However, Tan et al [3] reported that monitoring Cho of malignant breast lesions did not appear to be a robust way of predicting response to chemotherapy. Therefore, further investigations are required to determine whether early prediction previously reported holds in more patients using the current treatment protocol. We evaluated the feasibility of using quantitative ^{1}H-MRS to predict ultimate tumor response to neoadjuvant chemotherapy.

Methods

Twenty-three patients with biopsy-confirmed breast cancer who elected to receive neoadjuvant chemotherapy were included in this MR study. The examinations were performed on a Philips Eclipse 1.5 T MR system with the dedicated bilateral breast coil. MR imaging and ^{1}H-MRS were performed prior to treatment as the baseline then at 2 follow-up times, F/U-1 after 1-2 cycle of AC, and F/U-2 after 4 cycles AC or 2 cycles AC followed by first taxane regimen. All patients had the last F/U-3 after completing all chemotherapy, and based on whether there was residual disease the patient was determined as a (clinical complete) responder, or a non-responder. The single-voxel ^{1}H-MR spectra were acquired with TR/TE= 2000/270 ms, and 128 acquisitions for averaging (24 averages for reference). 17 of 23 patients were Cho-positive (signal-to-noise ratio > 2) in the baseline study before treatment. The absolute Cho concentration in malignant breast tumors was calculated with Eq. (1) and was expressed as a concentration in units of mmol/kg, details in [1]. The f_{T1} and f_{T2} factors in Eqs (2) and (3) were for correction of T_1 and T_2 relaxation times, respectively. The used T_2 relaxation times were 269 ms for Cho, and 97 ms for water. The T_1 relaxation times were 1513 ms for Cho, and 746 ms for water [4].

$$[Cho] = \frac{n_{H_2O}}{n_{Cho}\, MW_{H_2O}} \times \left(\frac{S_{Cho}}{S_{H_2O}} \times \frac{\sqrt{NS_{H_2O}}}{\sqrt{NS_{Cho}}} \right) \times \left(\frac{f_{T_1 H_2O}}{f_{T_1 Cho}} \times \frac{f_{T_2 H_2O}}{f_{T_2 Cho}} \right) \quad (1), \qquad f_{T_1} = 1 - \exp(-TR/T_1) \quad (2), \qquad f_{T_2} = \exp(-TE/T_2) \quad (3)$$

Results

7 of 13 patients who were complete responders had positive Cho before treatment. The median percentage change in Cho levels after 1-2 cycle AC was -36% (48% - 100 %, Fig. 1; Left), while the median percentage change in lesion size was -17% (7% - 32%), as shown in Fig. 2 (Left). After completing the full course chemotherapy, all patients did not have positive Cho based on the criterion (i.e., Cho SNR > 2). The median percentage change in lesion size in F/U-2 study was -88% (69% - 100%). 10 patients had residual disease after all chemo, and were classified as non-responders. All 10 patients had a positive Cho at the baseline. There is no significant difference in Cho level at the baseline between responder and non-responder groups (2.99±2.24 vs. 2.51±2.27, p = 0.67). The median percentage change in Cho levels after 1-2 cycle AC was 6% (302% to -100%, Fig. 1; Right), while the median percentage change in lesion size was -8% (2% - 40%), as shown in Fig. 2 (Right). Of them, 1 patient showed increased Cho in F/U-2, 1 decreased but still positive, and the remaining 8 patients did not have detectable Cho. The median percentage change in lesion size in F/U-2 study was -62% (34% - 100%). There were no significant correlation between change in Cho level in F/U-1 and the change in lesion size in F/U-2 (r = 0.11 , p = 0.69), or differentiating between R vs. NR in F/U-3.

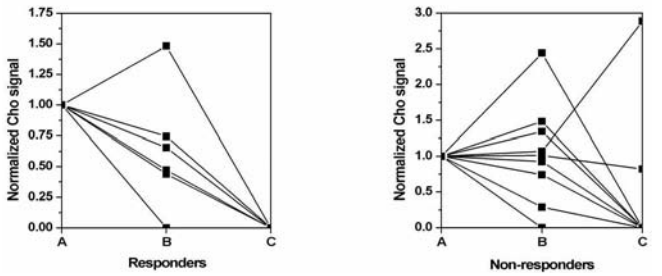

Figure 1: Change of normalized Cho levels with treatment in both responder and non-responder groups (x-axis index: A = baseline, B= F/U-1 after 1-2 cycle AC, and C= F/U-2 after 4 cycles AC or 2 cycles AC+taxane).

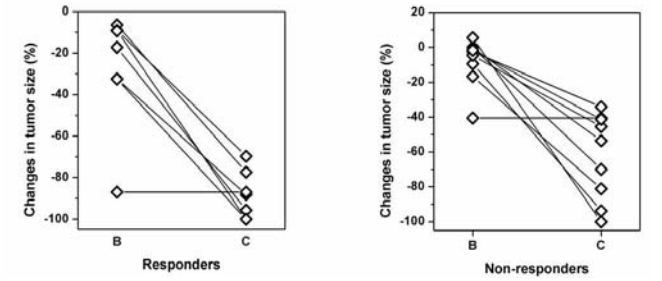

Figure 2: Change in lesion size after 1-2 cycle AC (B), and after 4 cycles AC or 2 cycles AC+taxane (C) in responder and non-responder groups.

Discussion

In this present study, 13/23 patients achieved a complete response (Responders) after all chemo, and among them 6 did not show elevated baseline Cho before treatment, and 6 showed reduced Cho level in F/U-1, and no Cho peak in F/U-2. 10/23 patients did not achieve a complete response (Non-responders), but in fact most of them had greatly down-staged tumors. Among them, all 10 had baseline Cho, and 2 had residual Cho in F/U-2. Although the change in Cho level (-36% vs. 6%) or lesion size (-17% vs. -8%) in F/U-1, (-88% vs. -62%) in F/U-2 was greater in the R than the NR group, not reaching significant level. The result suggests that a greater reduction in Cho or size after 1-2 cycle AC is more likely to show a final complete response, but they are not sensitive to distinguish between R vs. NR. Our finding is consistent with the previously reported findings by Tan et al [3]. As the neoadjuvant chemotherapy protocol becomes more sophisticated, it is very likely that most tumors would respond to some extent. The cocktail approaches used first-line and second-line regimen, each with combined drugs to target certain clones in a tumor to reach the optimal efficacy. Cho may reflect the change in the overall proliferation status, but it was unlikely to be directly associated with predictable response after completing all regimens, as demonstrated in this study. While the changes of Cho during therapy may be drug-dependent, the baseline Cho before therapy may provide some values. Most published literature findings were using treatment protocols to down-stage tumor, and as such interpretation of new findings with published results should note this change of emphasis.

References 1. Bolan et al., MRM 50: 1134-1143 (2003). 2. Meisamy et al. Radiology 236(2):465-75 (2005). 3. Tan et al., Proc. ISMRMI 14:574 (2006).

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