Proton MR spectroscopy for monitoring early treatment response of breast cancer to neo-adjuvant chemotherapy

With respect to treatment monitoring, conventional modalities such as physical examination, ultrasonography, and mammography are frequently used, but vary in reliability for measuring tumor’s therapeutic response [1, 2]. Magnetic resonance imaging (MRI) is increasingly being used to evaluate locally advanced breast cancer undergoing neo-adjuvant chemotherapy. However, changes in lesion size or dynamic contrast enhanced MRI are not detected until several weeks following chemotherapy [3].

Recently, proton magnetic resonance spectroscopy ($^1$H-MRS) has been proven helpful for the diagnosis of breast cancer based on total choline-containing compounds (tCho). The presence of tCho may indicate active cell replication, thus can be used for diagnosis. The role of $^1$H-MRS at 1.5 T for therapy response prediction is less established [4, 5]. Authors of this earlier study did not categorize which patients had a change in tCho signal nor did they describe when the change in the signal occurred. In this study, we applied longitudinal quantitative $^1$H-MRS using the internal reference method to monitor the change of tCho level during the full course of neo-adjuvant chemotherapy. The aim of our study was to determine whether the early changes can predict clinical response in women undergoing neo-adjuvant chemotherapy.

Twenty breast cancer patients (range 32–76 years old, mean 50 years) enrolled from June 2004 to December 2006, who were scanned with the MRI/MRS protocol, were included in this study. The inclusion criteria were patients with biopsy-confirmed diagnosis of malignant lesions that measured 2.4 cm or larger on MR images. All patients received biweekly doxorubicin (adriamycin) and cyclophosphamide (AC) as their first-line regimen. After the first two cycles, an oncologist evaluated patient response using all information available at that time (clinical examination, patient’s tolerance, sonography, etc), and the oncologist decided whether the patient should continue to receive two additional cycles of AC or should be switched to a taxane-based regimen. In all patients, MRI and $^1$H-MRS were performed before treatment as the baseline, then at least two follow-up (F/U) times, F/U-1 after one to two cycles AC and F/U-2 after four cycles AC or two cycles AC followed by the first cycle of a taxane regimen.

The MRI study was carried out using a 1.5 T Phillips Eclipse MR scanner with a standard bilateral breast coil (Philips Medical Systems, Cleveland, OH). The imaging protocol consisted of high-resolution precontrast imaging from the concerned breast, bilateral dynamic contrast-enhanced imaging, and $^1$H-MRS spectroscopy. For dynamic acquisition, the MR contrast agent gadodiamide (Omniscan®, GE Healthcare AS, Oslo, Norway, 1 cm$^3$/10 lbs body weight) was manually injected. After the MRI study was completed, single-voxel $^1$H-MRS was carried out using a point-resolved spin-echo sequence (PRsESS). The spectroscopic voxel was carefully positioned to maximize the coverage of the contrast-enhanced lesions while minimizing the inclusion of adipose tissue. The voxel size was from 2.4 to 8.0 ml. The absolute tCho concentration was analyzed using as an internal reference method [6]. Tumor size was measured by a radiologist based on the maximum intensity projection of the contrast subtraction images. Based on the one-dimensional RECIST criteria [7], patients were categorized into one of two groups: responders or nonresponders. Responders were defined as subjects with ≥30% one-dimensional tumor size reduction at F/U-2 compared with the baseline. Nonresponders were patients with a <30% of tumor size or no change.

In this study, 14 of 16 patients who were responders had positive tCho before treatment. There is no significant difference in tCho level at the baseline between responder and nonresponder groups (2.30 ± 2.24 versus 2.51 ± 2.27 mmol/kg, $P = 0.67$). The mean percentage change in tCho level after one to two cycles AC was −50%, while the mean percentage change in lesion size was −18% (Figure 1). After completing F/U-2, all patients did not have positive tCho. The mean percentage change in lesion size in F/U-2 study was −76%. Three patients were classified as nonresponders. All three patients had a positive tCho at the baseline. The mean percentage change in tCho level after one to two cycles AC was
−14%, while the mean percentage change in lesion size was −15%. Of them, two patients showed increased tCho in F/U-2, and the remaining one patient showed decreased tCho but was still positive. The mean percentage changes in tCho level and lesion size in F/U-2 study were 3.3% and 27%, respectively.

For the responder group, significant reductions in tCho level and tumor size were observed at the early F/U-1 with respect to the baseline ($P < 0.002$, $P < 0.008$), whereas no significant change was observed for either in the nonresponder group.

As the therapeutic agents become more effective, more patients can achieve the pathological complete response which is expected to lead to a better prognosis. Our study carried out on breast cancer treated with chemotherapy showed that in the responder group the reduction in tCho level at the first follow-up (F/U-1, one to two cycles AC) was significantly higher compared with the reduction in the tumor size ($P < 0.005$). The result demonstrates that the metabolic changes were greater than the size changes, suggesting that they might have occurred before gross morphological changes. An early reduction of tCho level can be interpreted as reflecting the inhibition of cellular proliferation and the cytotoxic effect of chemotherapy. In addition, the tCho level showed significant reduction in the response group but not in the nonresponse group, suggesting an early response predictor. This finding suggests that a greater reduction in tCho at the F/U-1 may be associated with a final complete response, so they may help to predict pathological complete response.

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