Prediction of Response to AC Chemotherapy Based on Early Changes in Size and Pharmacokinetic Parameters After 1 Cycle Treatment

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Purpose:

The commonly used means of evaluating the chemotherapeutic response in breast cancer is the change in tumor size. For a solid tumor RECIST is the current consensus criterion. It is known that clinical examination is highly subjective and can be inaccurate. Conventional imaging techniques such as mammography and ultrasound work well in cancers presented as mass type, but not in those presented as diffuse type. Furthermore, they may be difficult to differentiate residual disease from chemotherapy-induced fibrosis. MRI, with its high sensitivity, high spatial resolution, and 3-D coverage, has been proven as the most suitable modality for neoadjuvant chemotherapy monitoring in breast cancer. Not only that it can evaluate size, contrast enhancement kinetics can be measured during one imaging session; therefore the vascular information can be obtained without increasing much scan time. Therefore, it would be interesting to investigate whether the addition of vascular changes to the size change at early time after the therapy is initiated can achieve a higher accuracy in prediction of final response. We have an on-going study using the protocol with 2–4 cycles of AC (Doxorubicin and Cyclophosphamide) followed by Taxane-based regimen. Depending on the results of early and final AC response, the patients were separated into 4 groups: Group 1: R–R (responder after 1 AC, and also responder after 4 AC); Group 2: NR–R (non-responder after 1 AC, but responder after 4 AC); Group 3: NR–NR (non-responder after 1 AC, still non-responder after 4 AC); Group 4: NR–T (non-responder after 1 AC, and was switched to Taxane regimen after 2 AC). The results were compared among these 4 response groups, and also between responders (Groups 1+2) and non-responders (Groups 3+4). We would like to answer 2 questions: 1) whether the early changes observed in tumor size and/or in pharmacokinetic parameters are different between these 4 groups with different response patterns? 2) What is the performance of changes in tumor size and/or pharmacokinetic parameters after 1 AC predict the final outcome?

Methods:

Twenty-nine patients (29-75 yo) with histological-proven invasive breast cancer, who elected to receive neoadjuvant chemotherapy, were included in this study. Patients were recruited from May 2002 to Oct 2005 and chose to receive neoadjuvant chemotherapy either due to inoperable tumor or with clinically documented lymph node involvement. Twenty patients received 4 cycles of AC before switched to Taxane regimen or surgery. The remaining 9 patients only received 2 cycles of AC, and were switched to Taxane regimen earlier due to a lack of response based on clinical examination and/or other imaging findings. All patients had at least 2 MRI examinations, a baseline MRI prior to initiation of neoadjuvant chemotherapy and a follow-up MRI after 1 cycle of AC regimen (F/U-1). For those 20 patients who received 4 cycles AC, the second F/U MRI (F/U-2) was performed after 4 cycles of AC to determine their final response to AC treatment. The tumor size was measured from the MIPs (Fig. 1). The product of longest and perpendicular dimension was calculated as the tumor area (size). The responder is defined as 28% reduction after 1 AC (15% 1-D reduction) or 50% after 4 AC (30% 1-D reduction). Fig. 1 shows the enhancement kinetics from a NR-R and a NR-NR case. Although both were NR after 1 AC, the one showed flattened kinetics after 1 AC turned out to be R; and the one showed more wash-out remained as a NR. The kinetics was analyzed with Toft's 2-comparmental model to obtain K^{trans} and k_{ep}. The differences in 3 parameters were compared between 4 groups.

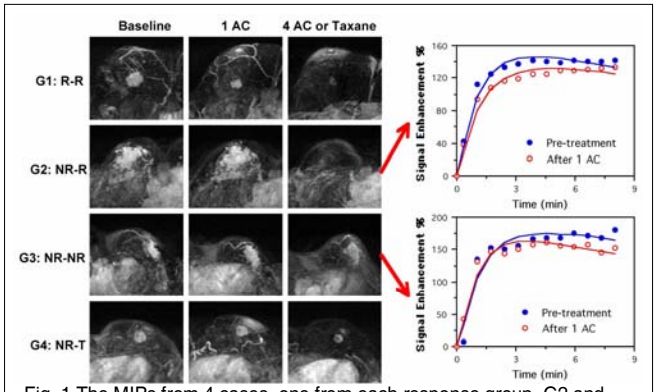

Fig. 1 The MIPs from 4 cases, one from each response group. G2 and G3 were NR after 1 AC, but turned to be R or remained as NR. The enhancement kinetics from the G2 and G3 cases are shown.

Results:

Of these 29 patients, 9 were R-R(G1), 8 were NR-R(G2), 3 were NR-NR(G3), 9 were NR and switched to taxane after 2AC(G4). Therefore all together there were 17 responders (G1+G2) and 12 non-responders (G3+G4). Fig. 2 shows the changes in 2-D tumor area, K^{trans}, and k_{ep} after 1 cycle AC compared to baseline in 4 groups. All patients in G1 showed greater than 28% tumor area reduction, and all patients in Groups 2-4 showed less than 28% reduction. Only one patient (1/9) in G1 showed increased K^{trans} and subjects in Groups 2-4 showed varying changes. Two subjects (2/9) in G1 showed increased k_{ep}, and all 3 (3/3) subjects in G3 showed increased k_{ep}. Fig. 3 shows the correlation between percent changes in tumor size and pharmacokinetic parameters after 1 cycle of AC. Both K^{trans} ($r = 0.48$, $p < 0.01$) and k_{ep} ($r = 0.65$, $p < 0.001$) were significantly correlated with tumor size changes. Lastly since the vascular changes were correlated with size changes, we were interested in investigating whether the vascular changes can improve the prediction of final response. ROC analysis was performed to differentiate responders (G1+G2) and non-responders (G3+G4). The area under the ROC curve was 0.877 for size change, 0.618 for K^{trans} and 0.760 for k_{ep}, 0.882 for size + K^{trans}, 0.904 for size + k_{ep}.

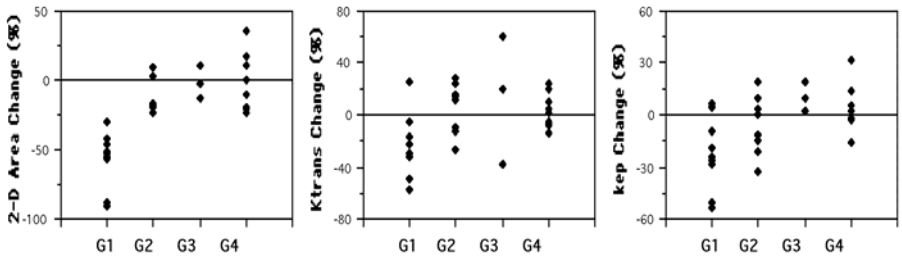

Fig.2 The changes of tumor size, K^{trans} and k_{ep} measured after 1AC compared to the baseline in 4 groups.

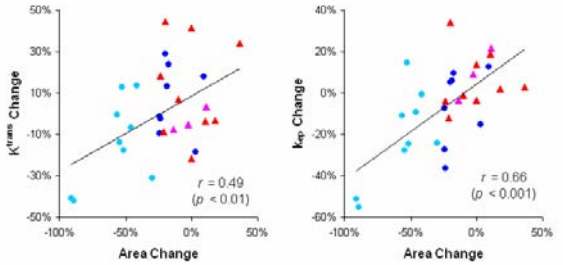

Fig.3 correlation between changes in K^{trans} and k_{ep} with size change Group-1 (●), Group-2 (●), Group-3 (▲), Group-4 (▲)

Discussion:

In this study we measured the tumor size change, and the changes of vascular pharmacokinetic parameters after 1 cycle AC, and investigated whether they can predict the final response to AC. The most interesting comparison was between G2 (NR after 1AC but became R) and G3 (NR after 1 AC and remained as NR). If we could separate them, it would help to determine who should receive the full 4 cycles to get the maximal benefit, and who should be stopped at 2 AC to allow early switch to taxane. Since we only had 3 patients in G3, not enough for making conclusive suggestions. However, all 3 showed increased k_{ep} after 1 AC, which may suggest non-responder. We also found that size and vascular changes were correlated; however, the area under ROC could be improved by adding K^{trans} or k_{ep} to size (AUC= 0.882, 0.904) compared to that using size alone (AUC=0.877). Therefore, although the early vascular changes are inferior than the size changes in prediction final AC response, since they can be collected in one study without increasing much scan time, they may provide additional information to help improve prediction accuracy.

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