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The use of breast imaging for predicting response to neoadjuvant lapatinib, trastuzumab and their combination in HER2-positive breast cancer: Results from Neo-ALTTO

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Abstract

Aim—To determine the value of mammography and breast ultrasound (US) in predicting outcomes in HER2 positive breast cancer patients (pts) within Neo-ALTTO trial.

Patients and methods—Mammography and US were required at baseline, week 6 and surgery. Two independent blinded investigators reviewed the measurements and assigned the corresponding response category. Pts showing complete or partial response according to RECIST (v1.1) were classified as responders. The association between imaging response at week 6 or prior to surgery was evaluated with respect to pathological complete response (pCR) and event-free Survival (EFS).

Results—Of the 455 pts enrolled in the trial, 267 (61%) and 340 (77%) had evaluable mammography and US at week 6; 248 (56%) and 309 (70%) pts had evaluable mammography and US prior to surgery. At week 6, 32% and 43% of pts were classified as responders by mammography and US, respectively. pCR rates were twice as high for responders than non-responders (week 6: 46% versus 23% by US, $p < 0.0001$; 41% versus 24% by mammography, $p = 0.007$). Positive and negative predictive values of mammography and US prior to surgery were

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Conflict of interest statement

None declared.

37% and 35%, and 82% and 70%, respectively. No significant correlation was found between response by mammography and/or US at week 6/surgery and EFS.

Conclusions—Mammography and US were underused in Neo-ALTTO although US had the potential to assess early response whereas mammography to detect residual disease prior to surgery. Our data still emphasise the need for further imaging studies on pts treated with neoadjuvant HER2-targeted therapy.

Keywords

HER2 positive breast cancer; Targeted therapy; Neoadjuvant; Mammography; Breast ultrasound

1. Introduction

The HER2 gene is amplified and/or overexpressed in approximately 20% of breast cancers, and historically has been associated with poor prognosis [1]. The introduction of dual anti-HER2 combinations, i.e. trastuzumab plus lapatinib or trastuzumab plus pertuzumab, has dramatically improved the clinical outcome of meta-static patients, raising hopes for their potential use also in the peri-operative setting. The Neo-ALTTO study showed higher pathological complete response (pCR) rates with trastuzumab plus lapatinib with paclitaxel as compared with either trastuzumab or lapatinib alone with paclitaxel (51.3% versus 29.5% or 24.7%, respectively; $p < 0.01$ for both) [2]. Likewise, the Neosphere study showed increased pCR rates by the addition of pertuzumab to trastuzumab and docetaxel (45.8% versus 29.0%, p 0.014) [3]. However, none of these studies was powered to detect an improvement in event-free survival (EFS), though in both studies pCR was significantly associated with longer EFS [4,5].

Ideally, a patient's response to neoadjuvant therapy could be used to individually tailor systemic treatment. The GeparTRIO trial randomised breast cancer patients showing sub-optimal (i.e. <50%) response to two cycles of neoadjuvant anthracycline- and taxane-based chemotherapy, to further four cycles of the same regimen or to an alternative treatment with vinorelbine and capecitabine. An exploratory analysis of long-term survival data from this study found that response-guided neoadjuvant chemotherapy appears to improve disease-free survival and overall survival [6]. Additional evidences are anyway needed to prove the clinical benefit of this approach. Evidence on imaging performance in monitoring pCR according to breast cancer is lacking, especially when considering the different breast cancer subtypes. Non-invasive imaging methods that can accurately determine pCR after a short course of HER2-targeted therapy would be of great value in the design of clinical trials that test different treatment types or duration based on response to neoadjuvant therapy. Common imaging modalities used in the evaluation of patients with primary breast cancer include mammography and ultrasound (US). There is extensive literature on the use of these modalities in measuring breast primary tumours and the extent of residual disease after therapy [7–11]. However, clinical studies assessing the value of mammography and US in predicting pCR and long-term clinical outcome in the context of large, randomised trials are few. In this sub-study, we aimed to investigate the potential role of mammography and breast US in predicting pCR and EFS in the Neo-ALTTO trial.

2. Materials and methods

Details on the Neo-ALTTO study (Breast International Group 1-06) and its results have been extensively published elsewhere [2,4]. In brief, Neo-ALLTO was a multicentre randomised phase III study in which HER2 positive breast cancer patients with primary breast tumours greater than 2 cm in diameter by either mammography or US were assigned to lapatinib (154 patients), trastuzumab (149 patients), or lapatinib plus trastuzumab (152 patients) for 6 weeks (i.e. biological window), followed by other 12 weeks with the addition of weekly paclitaxel. Surgery was performed within 4 weeks from the last dose of paclitaxel. Conventional imaging for primary tumour assessment was performed with both mammography and US at baseline, week 6 and prior to surgery. Central review was not required per protocol for either mammography or US. However, two distinct investigators (SDC and AAH) blinded to treatment assignment and patient's outcomes, independently reviewed radiological measurement of primary tumours and defined objective tumour response according to the RECIST (v.1.1) categories for primary breast tumour [12,13]. Patients showing either complete or partial response (CR and PR, respectively) were classified as responders. Early responses were defined as either CR or PR at week 6, whereas late responses were defined as either CR or PR prior to surgery. pCR at surgery was defined as for the primary end-point of Neo-ALLTO, which is the absence of invasive tumour cells in the breast.

2.1. Statistical analysis

The analysis was performed on all patients enrolled in the Neo-ALTTO trial with at least one evaluable mammography and/or US. Exploratory analyses tested the difference in objective response between treatment arms (χ^2 test). Univariate survival models, including hormone receptor (HR) status and treatment as covariates in cox proportional hazards model, were used to test the relationship between objective response recorded by imaging and EFS, defined as the time from random-isation to the first event. For women who received surgery for breast cancer, events could be breast cancer relapse after surgery, second primary malignancies, or death without recurrence. For women who did not have surgery for breast cancer, events could be death during clinical follow-up or non-completion of any neoadjuvant investigational product because of disease progression. Patients who had pCR measurement were included in the analysis (χ^2 test) of pCR rates among responder and non-responders. Logistic regression modelled the relationship between imaging modalities and pCR, and models were adjusted for treatment and HR status. Patient demographics and tumour characteristics such as age, histologic type, hormone receptor status, and given treatment were analysed.

3. Results

3.1. Study population

Of the 455 patients enrolled in the trial, 267 (61%) and 340 (77%) had evaluable mammography and US at week 6, while 248 (56%) and 309 (70%) had evaluable mammography and US at surgery. Ultimately, 279 and 207 patients had both mammography

and US at week 6 and surgery, respectively. Table 1 shows the main patient clinical features, including stratification factors and treatment.

3.2. Objective tumour response at week 6 and surgery

Early responses were observed in 85 patients (32%) evaluated by mammography and in 148 patients (43%) evaluated by US, whereas late responses were observed in 172 women (69%) evaluated by mammography and 242 patients (78%) evaluated by US. The agreement between mammography and US was fair (kappa range 0.21–0.4) to moderate (0.41–0.6). Using US as imaging modality, objective responses in the primary tumour according to treatment arm at week 6 were as follow: 57 (48%), 29 (27%) and 62 (54%) for lapatinib, trastuzumab and combination arms, respectively ($p < 0.001$); at surgery, responses were 86 (80%), 74 (74%) and 82 (81%) for lapatinib, trastuzumab and combination arms, respectively ($p = 0.428$). Using mammography as imaging modality, responses at week 6 were 30 (32%), 18 (22%) and 37 (41%) for lapatinib, trastuzumab and combination arms, respectively ($p = 0.031$); at surgery, responses were 59 (70%), 48 (61%) and 65 (76%) for lapatinib, trastuzumab and combination arm, respectively ($p = 0.091$). Radiologic responses by treatment arm and imaging modality are summarised in Table 2.

No significant association was found between any tumour or patient characteristics and imaging response, with the only exception of HR status. Objective tumour responses were higher in patients with HR-negative tumours than in patients with HR-positive tumours: at week 6, 82 (49%) versus 66 (39%), respectively, by US ($p = 0.065$); 52 (39%) versus 33 (25%), respectively, by mammography ($p = 0.014$). Similar results were observed at surgery: 123 (81%) versus 119 (76%), respectively, by US ($p = 0.274$) and 97 (76%) versus 75 (62%), respectively, by mammography ($p = 0.014$; Table 3).

3.3. Correlation between objective tumour response and pCR

When considering the imaging response observed at week 6, pCR was reported in 35/85 and 44/182 patients with and without mammography response, respectively (41% versus 24%, $p = 0.005$). Similarly, pCR was reported in 68/148 and 45/195 women with and without US response, respectively (46% versus 23%, $p < 0.001$). Hence, pCR rates were significantly higher for early responders compared to non-responders considering both mammography and US (Table 4). No correlation was found between pCR and radiologic complete responses at surgery (57% by US and 53% by mammography; Table 5). Positive predictive and negative predictive values of mammography and US prior to surgery were 37% and 35%, and 82% and 70%, respectively. Results did not change according to HR status (data not shown). Both imaging modalities were able to predict pCR at week 6, whereas only mammography was able to predict pCR prior to surgery (Table 6).

3.4. Correlation between objective tumour response and EFS

At a median follow-up of 7 years, with a total of 64 events, at univariate analysis, no significant correlations between tumour response and EFS could be identified with either modality at week 6 or at surgery (Table 7).

4. Discussion

Although HER2-targeted therapy improved clinical outcome of patients both in the early and advanced settings, so far not a single biomarker beyond HER2 has been validated to identify those patients most likely to benefit from single or dual blockade. The accuracy of different radiological modalities in predicting pCR at surgery and/or long-term outcomes remains unclear. Indeed, few data exist in the medical literature about this topic and, to the best of our knowledge, no studies have specifically focused on the HER2-positive sub-population yet.

In the present work, we found a correlation between early response by imaging and pCR. The pCR rate was twice higher in patients with CR or PR by US or mammography at week 6 compared to those non-responders. Although not statistically significant, HR-positive patients were less likely to be classified as early responders than HR-negative patients. This finding, which must be carefully weighed due to the small number of patients in each subgroup, confirms the low rate of treatment response of HR-positive disease, already documented by previous studies and underlines the need of alternative intermediate end-points or timing of evaluation in such population. The lack of association between radiological response and EFS is not surprising, as Neo-ALTTO was not powered to detect differences in long-term outcomes. Also, the high prevalence of HR-positive patients in the study population may have contributed to this result, given the well documented lack of correlation between pCR and disease outcome in HR-positive cases.

The second interesting observation concerns the lack of overlap between mammography and US in predicting pCR. In particular, the analysis of the PPVs and NPVs of these imaging modalities allows to conclude that US shows a better accuracy profile in week 6 evaluation, whereas mammography appears to be more useful in the pre-surgery context. This observation may entail practical implications in defining the role of each specific imaging modality, with the purpose of optimising the monitoring of disease response during neoadjuvant treatment. Because of its better performance in mid-course evaluation, breast US may be better used to assess early response to treatments, identifying patients potentially taking advantage of a change in therapeutic plan or even a direct access to surgery; however, its value needs to be prospectively demonstrated. Indeed, many studies are evaluating the possibility of modifying treatment in cases lacking an optimal clinical response during pre-operative treatment [6]. On the other hand, given its NPV at week 18 evaluation, mammography seems to be more accurate in detecting residual disease at surgery, with profound implications in the choice of the surgical approach and in the prediction of histological findings. Moreover, recent studies are investigating the potential benefits of adjuvant chemotherapy in patients obtaining an unsatisfactory pathological response to neoadjuvant treatments. The strongest evidence has been achieved in the triple negative disease in which poor response to primary chemotherapy and unfavourable histological prognostic findings are known to implicate an extremely high probability of relapse [14]. If these data were confirmed in HER2-positive breast cancer too, pre-surgical mammography evaluation could become a fundamental step in predicting the need of postoperative treatments, with the goal of planning an optimal patient-tailored therapeutic strategy. The differential accuracy profile of mammography and US in this population suggest an

adjunctive consideration. As per protocol, patients enrolled in Neo-ALLTO received initial 6 weeks of anti-HER2 treatment alone, followed by combined weekly paclitaxel and the same anti-HER2 agent for further 12 weeks (total treatment duration: 18 weeks). Thus, imaging evaluation at week 6 specifically reflects tumour response to targeted treatment in this experimental setting. In that regard, Neo-ALLTO can be considered a particularly favourable setting to study tumour response to biological agents, comparing the accuracy of different imaging modalities. Further implications and potential clinical applications of these findings need adjunctive research to be clarified.

It is worth to notice that 6-week responses with both mammography and US were significantly lower in the trastuzumab arm, than in the lapatinib and lapatinib + trastuzumab arms. Nonetheless, Neo-ALLTO demonstrated that the final rate of pCR was not different between trastuzumab and lapatinib. This may have been because of differences in the pharmacokinetic profile of these anti-HER2 agents which reach steady state concentration at very different times, few days for lapatinib and few months for trastuzumab [15,16]. Nevertheless, pioneer studies in the metastatic setting reported similar median time to response for lapatinib and trastuzumab, i.e. 7.9 and 6 weeks, respectively [16,17]. More recently, neoadjuvant studies showed that one-third of all responses to lapatinib occurred by week 4 and 55% by week 8; and half of responses to trastuzumab plus chemotherapy by week 6, with a range of 3–25 weeks [17–19]. Hence, we cannot exclude that the higher rate of early response with lapatinib may lie in the inherent mechanism of action of this compound as compared with trastuzumab or rather in the profile of the tumour.

Finally, we observed that a relatively small proportion of women had evaluable examinations at week 6 and before surgery. The intermediate course evaluation was less frequently performed than the pre-surgery, and more patients had breast US than mammography. These results seem to suggest a relative underuse of imaging modalities in evaluating disease response during neoadjuvant treatment. Moreover, the most considerable amount of data in this setting concern the use of methods such as positron-emission tomography (PET) and magnetic resonance imaging (MRI), which are remarkably expensive, more complicated and less widespread than mammography and US [20–26].

At this regard, functional imaging techniques such as MRI and PET, that permit evaluation of residual viable tumour after neoadjuvant therapy by detecting changes in tumour vascularity and metabolism, are useful tools in evaluating the patient during and after the completion of treatment. A recent meta-analysis reported that the diagnostic performance of MRI is similar to that of PET for the assessment of breast cancer response to neo-adjuvant therapy. However, PET is more sensitive than anatomic MRI for that purpose; in addition, PET is superior to MRI in assessing response early on treatment [27]. A previous Neo-ALLTO sub-study investigating the role of fluorodesoxyglucose (FDG) PET in predicting pCR documented that metabolic response at week 2 highly correlated with that at week 6. Moreover, mean standard uptake volume (SUV) reduction predicted the probability of pCR [20]. According to these data, FDG PET seems to be superior to conventional imaging, and different studies are currently ongoing to prospectively evaluate the value of FGF PET imaging in HER2 breast cancer patients. The absence of clear guidelines on this topic probably gives a determinant contribution to the heterogeneous clinical approach observed.

Breast US seems to predict slighter better the chance of pCR than mammography at week 6 and perhaps should become the preferred modality of early assessment with the benefit of not having radiation involved. Also, the results observed at surgery make one to wonder the validity of performing a tumour evaluation at surgery for those cases where mastectomy is clearly indicated. This approach would decrease both the radiological burden for the patients and the financial burden for the society.

Some important limitations of our study have to be underlined. It constitutes a retrospective analysis, which investigates end-points not pre-specified in the design of Neo-ALLTO trial. Moreover, a limited number of patients had evaluable mammography and US at baseline, week 6 and surgery. Thus, the analysis focuses on a relatively small subgroup of the patients enrolled in the trial, and this may have hampered the possibility to obtain significant conclusions. Despite these drawbacks, the present work supports the potential role of mammography and US in monitoring early disease response in HER2 positive BC patients treated with neoadjuvant anti-HER2 therapies.

In conclusion, our results confirm the urgent need of evidence-based data about the critical topic of monitoring disease response during neoadjuvant treatments. Clinical trials with clearly defined radiological endpoints should be prioritised in order to optimise health resources and to maximise breast cancer patients' chances to be optimally treated.

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Table 1

Baseline patient and tumour characteristics.

	US at week 6, N = 340	US at surgery, N = 309	MMG at week 6, N = 267	MMG at surgery, N = 248
Age (years)	N (%)			
<65	300 (88.24)	271 (87.70)	237 (88.76)	219 (88.31)
≥65	40 (11.76)	38 (12.30)	30 (11.24)	29 (11.69)
Treatment	N (%)			
Lap	119 (35.00)	108 (34.95)	94 (35.21)	84 (33.87)
Trast	107 (31.47)	100 (32.36)	82 (30.71)	79 (31.85)
Lap + Trast	114 (33.53)	101 (32.69)	91 (34.08)	85 (34.27)
HR status	N (%)			
Positive	171 (50.29)	157 (50.81)	133 (49.81)	121 (48.79)
Negative	169 (49.71)	152 (49.19)	134 (50.19)	127 (51.21)
cN	N (%)			
N0/1	287 (84.41)	265 (85.76)	216 (80.90)	206 (83.06)
N ≥ 2/X/missing	53 (15.59)	44 (14.24)	51 (19.10)	42 (16.94)
cT	N (%)			
T2	214 (62.94)	193 (62.46)	152 (56.93)	142 (57.26)
T = 3	126 (37.06)	116 (37.54)	115 (43.07)	106 (42.74)
Planned surgery	N (%)			
Mastectomy	245 (72.06)	210 (67.96)	200 (74.91)	176 (70.97)
BCS	95 (27.94)	99 (32.04)	67 (25.09)	72 (29.03)

Abbreviations: cN: clinical nodal status; cT: clinical tumour size; HR: hormone receptors; Lap: lapatinib; Lap + Tras: lapatinib + trastuzumab; Tras: trastuzumab; MMG: mammography; BCS: breast-conserving surgery; US, ultrasound.

Table 2

Radiologic responses by treatment arm and imaging modality.

	Lap	Trast	Lap + Trast	χ^2 value
US at week 6	57 (48%)	29 (27%)	62 (54%)	<0.001
MMG at week 6	30 (32%)	18 (22%)	37 (41%)	0.031
US at surgery	86 (80%)	74 (74%)	82 (81%)	0.428
MMG at surgery	59 (70%)	48 (61%)	65 (76%)	0.091

Abbreviations: Lap: lapatinib; Lap + Tras: lapatinib + trastuzumab; MMG: mammography; Tras: trastuzumab; US: ultrasound.

Table 3

Radiologic responses by HR status and imaging modality.

	HR+	HR−	χ^2 value
US at week 6	66 (39%)	82 (49%)	0.065
MMG at week 6	33 (25%)	52 (39%)	0.014
US at surgery	119 (76%)	123 (81%)	0.274
MMG at surgery	75 (62%)	97 (76%)	0.014

Abbreviations: HR+: hormone receptor status positive; HR−: hormone receptor status negative; MMG: mammography; US: ultrasound.

Table 4

pCR rates by radiologic response.

	pCR non-responders	pCR responders	χ^2 value
US at week 6	45 (23%)	68 (46%)	<0.001
MMG at week 6	44 (24%)	35 (41%)	0.005
US at surgery	20 (30%)	84 (35%)	0.456
MMG at surgery	14 (18%)	35 (41%)	0.004

Abbreviations: MMG: mammography; US: ultrasound; pCR, pathological complete response.

Table 5

pCR rates among radiologic complete responders.

	pCR	χ^2 value
US at surgery	35 (57%)	0.249
MMG at surgery	47 (53%)	0.596

Abbreviations: MMG: mammography; US: ultrasound; pCR, pathological complete response.

Table 6

Univariate analysis for prediction of pCR by radiologic response.

	Odds ratio (95% CI)	p value
Response by US		
Week 6	2.52 (1.53–4.16)	0.0003
Surgery	1.09 (0.59–2.03)	0.7803
Response by MMG		
Week 6	1.96 (1.10–3.49)	0.0234
Surgery	2.19 (1.11–4.32)	0.0241

Abbreviations: CI: confidence interval; MMG: mammography; US: ultrasound; pCR, pathological complete response.

Table 7

Univariate analysis of correlation between tumour response and EFS.

	Hazard ratio	p value
US at week 6	0.769	0.2344
MMG at week 6	1.040	0.8863
US at surgery	0.675	0.1149
MMG at surgery	1.396	0.2589

Abbreviations: MMG: mammography; US: ultrasound; EFS, event-free survival.