Review Article

Neoadjuvant therapy in operable breast cancer: Application to human epidermal growth factor receptor 2-overexpressing tumors

Chad Mohamed Amine, Zouhour Fadoukhair[1], Sami Brahmi, Nabil Smaili[2], Samia Arifi, Nawfel Mellas

Department of Medical Oncology, Hassan II University Hospital, Fez, [1]Department of Medical Oncology, National Institute of Oncology, Rabat, [2]Department of Medical Oncology, University Hospital of Marrakech, Marrakech, Morocco

ABSTRACT

Neoadjuvant (NA) chemotherapy is the standard of care for patients with large, inoperable tumors or inflammatory breast cancer, but it is also considered for women with operable disease. Several trials have demonstrated equivalent survival benefits for the administration of chemotherapy before or after surgery. Moreover, preoperative treatment allows a higher rate of breast conserving surgery. NA treatment with a sequential anthracycline-taxane based chemotherapy in combination with targeted human epidermal growth factor receptor 2 (HER2) therapy is the gold standard treatment for patients with HER2-positive breast cancer. This approach is based on the higher pathologic complete response (pCR) seen with the addition of trastuzumab. The pCR can be increased with dual HER2-receptor blockade and chemotherapy. Patients with a pCR after chemotherapy and trastuzumab showed a significantly better outcome. This review, based on an exhaustive summary of current literature, highlights the benefits of NA systemic therapy in HER2 positive operable breast cancer.

Key words: Breast cancer, human epidermal growth factor receptor 2 overexpressing, neoadjuvant treatment

INTRODUCTION

Neoadjuvant (NA) therapy in women with early breast cancer improves rates of operability in locally advanced disease and breast conservation in women who would otherwise require a mastectomy.[1] However, meta-analyses of NA trials have not shown an improvement in disease-free survival (DFS) or overall survival (OS) compared to similar treatment delivered after breast surgery.[2] Human epidermal growth factor receptor 2 (HER2) amplification is seen in approximately 20% of breast cancers and is associated with more aggressive disease and worse prognosis.[3] Trastuzumab, a monoclonal antibody against the extracellular component of the HER2 protein, results in improved DFS and OS in patients with HER2-overexpressing tumours in both the adjuvant and metastatic settings.[4] In the NA setting, the achievement of pathologic complete response (pCR) with chemotherapy plus trastuzumab was correlated to improved survival outcomes.[4] More recently, additional HER2-targeted therapies including lapatinib (a tyrosine kinase inhibitor) and pertuzumab (a humanised anti-HER2 monoclonal antibody) have shown good results in metastatic breast cancer leading to the exploration of dual blockade with a combination of targeted therapies in the NA setting.[5,6] This review will summarize the benefits of NA systemic therapy in HER2-positive operable breast cancer.

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RATIONALE FOR NEOADJUVANT THERAPY IN OPERABLE BREAST CANCER

Neoadjuvant systemic treatment also known as preoperative systemic treatment is being used in the management of breast cancer. It was initially reserved for patients with inoperable inflammatory and locally advanced breast cancer. But it is now considered an option for patients presenting with an operable breast cancer especially for

Address for correspondence: Dr. Zouhour Fadoukhair, Department of Medical Oncology, National Institute of Oncology, Rabat 10000, Morocco, North Africa. E-mail: zouhour.fa@hotmail.com

those with triple-negative or HER2-positive disease, in which we expect a high pCR.[1]

There are several potential benefits for the use of NA treatment for early-stage breast cancer. Once the long-term benefits of adjuvant therapy were recognized, it was postulated that administration of chemotherapy prior to surgery might be more effective for eradicating micrometastatic disease and therefore could result in improvements in long-term outcomes.[2] Also, NA chemotherapy improves rates of breast conservation.[2] Moreover NA therapy provides an *in vivo* model to assess the response of tumour to the treatment. In the adjuvant setting, regimens are empirically used, but there is no way to assess response since all visible tumors have been removed. pCR is considered as a surrogate marker of survival.[1] Further, the NA setting provides the opportunity to examine modulation of tissue biomarkers from the time of biopsy to the time of definitive breast surgery following completion of preoperative systemic therapy.[2]

Neoadjuvant versus adjuvant chemotherapy

Several trials have demonstrated equivalent survival benefits from the administration of chemotherapy before or after surgery. Because of the possibility that NA chemotherapy may improve outcome by exposing micrometastases to early chemotherapy, NA therapy was investigated in patients with primary operable disease.[4] The pioneer trial investigating these issues was the B18 trial of the National Surgical Adjuvant Breast and Bowel Project (NSABP).[3] In this study, 1523 women with operable breast cancer were randomized to four cycles of adriamycin, cyclophosphamide (AC) before or after definitive surgery. In the NA group, 80% of the patients had a clinical complete response (CR) or partial response (PR). A pCR, which was defined as the absence of malignant tumor cells at the site of the primary tumor irrespective of nodal status, was seen in 13% of the patients. In contrast to the adjuvant group, the number of patients with positive nodes was significantly lower in the NA group (59 vs. 43%; $P < 0.001$). Furthermore, a higher rate of breast conserving treatment was observed with NA treatment versus adjuvant treatment (67 vs. 60%; $P = 0.002$). There were no significant differences in DFS and OS, even though updated results with follow-up of >15 years indicated a trend in favour of NA treatment in women younger than 50 years for DFS (hazard ratio [HR] 0.85; $P = 0.053$).[3,4] In women whose tumours achieved a pCR, the relapse free survival (RFS) rate was statistically higher (85.7%), compared with patients with residual pathologic invasive disease, clinical PR, or clinical no response (RFS of 76.9%, 68.1% and 63.9%, respectively; $P < 0.0001$). Other trials with integration of taxanes confirmed these results.[7,8] Finally, a meta-analysis of approximately 4000 patients enrolled in 9 trials of NA versus adjuvant chemotherapy or endocrine therapy showed no difference in distant disease recurrence or OS between NA or adjuvant therapy.[9] NA chemotherapy was associated with a higher breast conservation rate. However, there was an increased risk of locoregional recurrence in patients who received NA therapy, and did not achieve a pCR, it has been also attributed to omission of definitive local therapy in some of the NA trials. In this meta-analysis, pCR was associated with an improvement in OS and DFS.

Assuming that definitive local therapy will be provided, preoperative systemic therapy appears to be an acceptable alternative to standard postoperative systemic therapy of early-stage breast cancer, aiming breast preservation. It also facilitates development of new drugs for use in the NA setting is a worthwhile objective.

Predictors of response and selection of patient candidates to neoadjuvant treatment

In patients with operable disease, NA chemotherapy is a valid treatment option when mastectomy seems necessary but the patient wishes breast conserving surgery. Moreover the patient must fulfil the criteria of breast preservation. An international expert panel has recommended that clinicians should consider NA chemotherapy in any patient with primary operable disease for whom adjuvant chemotherapy is clearly indicated.[1] Patients diagnosed with HER2-positive disease usually need to be treated with chemotherapy and anti-HER2 directed therapy. NA treatment should be withheld only in patients with tumors <1 cm in diameter, a size for which no evidence from prospective clinical trials supports use of anti-HER2 directed therapy and the chemotherapy indication is uncertain.[10]

Also, the knowledge of the tumor stage and histologic features can help predict who will likely respond to NA treatment. Tumour characteristics that predict an improved response to NA chemotherapy include absent or low expression of estrogen receptor (ER), high Ki-67 or another proliferation index, high grade, HER2-overexpressing, triple negative and ductal pathology.

Patients who have a high likelihood of achieving a pCR with NA chemotherapy may be especially considered for NA treatment. pCR has been used as an endpoint in numerous trials of NA systemic therapy for breast cancer. It appears to be a reliable surrogate of long-term outcome, because several trials have shown that patients achieving a pCR have a more favorable outcome than those without a pCR. Thus, the lack of a pCR might indicate the need for a more intense surveillance program or induce development of new postsurgical treatment options. Improved response to NA chemotherapy and high pCR rates are more likely in women with HER2-positive or triple-negative breast cancer

compared to women with tumors that are low grade or those that express ER.[11,12]

Estrogen receptor status is an important predictive factor to achieve pCR in NA chemotherapy for operable breast cancer. Several reports have demonstrated that patients with ER-negative tumors are more likely to achieve pCR than those with ER-positive tumors for NA chemotherapy for operable breast cancer.[13]

However, there has not been a uniform definition of pCR, Some authors have defined pCR as the absence of both *in situ* and invasive cancer following NA chemotherapy,[14] whereas others have considered only the invasive component in the definition. Some investigators have defined pCR as absence of residual cancer in the breast and regional lymph nodes at the time of definitive surgery, whereas others have defined pCR as a CR in the breast, irrespective of axillary nodal involvement.[15] Noninvasive disease as the only remaining tumor tissue (ypTis ypN0) after NA chemotherapy is a rare event in HER2-negative disease, but is much more frequently in patients with HER2-positive tumors treated with chemotherapy and anti-HER2 agents. It was described that the highest HR for DFS and OS in patients with pCR versus without pCR was observed when no residual invasive and noninvasive tumor cells in the breast and in the axillary nodes.[16] Finally the adoption of a single term with a standard definition is needed to facilitate discussion.

SYSTEMIC NEOADJUVANT TREATMENT

Chemotherapy

Previously, NA chemotherapy trials used cyclophosphamide, methotrexate, and fluorouracil (CMF) and anthracycline-based regimens.[17,18] Thereafter trials have focused on the addition of taxanes. In the Aberdeen trial, 162 patients with a CR or PR to four cycles of an anthracycline-based regimen were randomized to four additional cycles of the same regimen or to four cycles of docetaxel. With a median follow-up of 65 months, women who were sequenced to docetaxel had an improved pCR rate compared to the anthracycline-treated women (34% and 16%, respectively, $P = 0.04$), an improvement that was correlated with an impressive OS benefit (95% for the docetaxel arm vs. 78% for the standard arm, $P = 0.04$).[19] The NSABP-27 trial randomized 2411 women with operable breast cancer (excluding patients with T4 tumors) to four cycles of AC alone, four cycles of AC followed by four cycles of docetaxel before surgery, and in the third arm to four cycles of NA AC followed by four cycles of adjuvant docetaxel after surgery. The addition of taxanes preoperatively to AC increased significantly the clinical CR rate (40 vs. 64%; $P > 0.001$), the pCR rate (14 vs. 26%; $P > 0.001$), and the proportion of patients with negative nodes (51 vs. 58%; $P > 0.001$) compared to four cycles of AC. However, despite the pCR rate being almost doubled by the addition of taxanes to AC preoperatively, the study did not demonstrate a significant improvement in outcome in terms of DFS and OS.[20] Other trials with taxanes have reported an improvement compared with anthracyclines alone.[21-23] Some studies tried to improve the results of NA chemotherapy by adding new cytotoxics, like gemcitabine, capecitabine or vinorelbin but in vain.[24-26]

The aforementioned results indicate that the standard NA chemotherapy remains a sequential anthracycline–taxane-based chemotherapy

Human epidermal growth factor receptor 2 targeted therapy

Human epidermal growth factor receptor 2 and oncogenesis

The targeting of growth factor receptors is one of the most successful field in cancer drugs development. Lot was learned from the observation that amplification of HER2 was associated with aggressive tumor behavior and poorer outcome than recorded in non-amplified cases of breast cancer.[4]

About 15–25% of breast cancers overexpress HER2,[27,28] a 185 kD glycoprotein encoded by a proto-oncogene HER2/neu (C-Erb2) localized on the long arm of chromosome 17 that is normally expressed in the epithelia of various organs such as lung, bladder, pancreas, breast and prostate.[29,30]

Human epidermal growth factor receptor 2 belongs to the Erb family of transmembrane receptor tyrosine kinases (RTKs) that have a major role in the signaling pathways by mediation of cell growth, differentiation, survival and signaling that regulates intercellular communication during development.[31,32]

The four members of the Erb family are epidermal growth factor receptor or HER1 (Erb-B1); HER2 (Erb-B2); HER3 (Erb-B3) and HER4 (Erb-B4). This closely related growth factor receptors, have three major domains: The ligand-binding domain, the transmembrane domain and the intracellular kinase domain.[33]

Several ligands have been recognised that bind HER1, HER3 and HER4 including transforming growth factor a, epidermal growth factor, primarily neuregulins and heregulins. No known natural ligand exists for HER2, but evidence suggests that HER2 is the preferred dimerization partner for activation of the other HER receptors. Growth factor binding triggers homo- or heterodimerisation initiating signal transduction.[34]

Signalling through HER-receptors family dimers leads to the activation of downstream signalling cascades (including PI3K-, Akt-, mammalian target of rapamycin mTOR- and mitogen-activated protein kinases MAPK-pathways) and signal transducers and activators of transcription which control cell cycle, cell growth and survival, apoptosis, metabolism and angiogenesis.[4]

That's why blocking the HER2 receptor or its key downstream effectors presents a great opportunity to strike tumoral cells, the first monoclonal antibody to inhibit signalling through HER2 homodimers was the trastuzumab, followed by lapatinib (a small molecule that inhibits HER1 and HER2 tyrosine kinase activities, pertuzumab which prevents HER2:HER3 dimer formation, trastuzumab emtansine (TDM1) [Table 1] and other molecules currently being investigated in clinical trials especially in HER2-resistant breast cancer additionally, HER2 status has been shown to be predictive for response to certain therapeutic.

Trastuzumab

Before the routine use of trastuzumab (a monoclonal antibody), HER2 overexpression was associated with a more aggressive tumor phenotype and worse prognosis (higher rate of recurrence and mortality), independent of other clinical features (age, stage, tumor grade).[1]

Trastuzumab, a monoclonal humanized antibody binding to the extracellular domain of HER2, is an established treatment for HER2-positive breast cancer, in the adjuvant and metastatic setting, and has been widely investigated in the NA setting.

The introduction of trastuzumab to the treatment of HER2-positive BC represented an important reform in the history of oncology. The pivotal study by Slamon *et al*. showed that the addition of trastuzumab to chemotherapy in metastatic breast patients significantly improved response rate (50% vs. 32%; $P < 0.001$), duration of response (9.1 months vs. 6 months; $P < 0.001$), and time to disease progression (7.4 months vs. 5.6 months; $P < 0.001$), with a significant 20% reduction in the risk of death (HR 0.80; $P = 0.046$).[35] Also, the addition of trastuzumab to adjuvant chemotherapy has resulted in a striking reduction in the risk of relapse and death by 50% and 30% respectively.[36-39] These results led to investigate trastuzumab in the NA setting.

Table 1: Therapeutic agents for HER-2 overexpressing breast cancer

Name	Class	Mechanism (s) of action
Trastuzumab	Monoclonal antibody	Acts at the extracellular domain, against HER-2 homodimers
Lapatinib	Small molecule TKI- reversible	Selective inhibitor of EGFR/HER1 and HER2 intracellular tyrosine kinase
Pertuzumab	Monoclonal antibody	Binds to different part of extracellular domain, Inhibits hetero-dimerization
T-DM1	Antibody-drug conjugate	Trastuzumab conjugated to an anti-microtubule agent (maytansine)

HER-2: human epidermal growth factor receptor 2, EGFR: Epidermal growth factor receptor

One of the first phase III trials in NA setting was conducted at the MD Anderson Cancer Center, and patients with stages II and IIIa HER2-overexpressing tumors randomized to four cycles of paclitaxel followed by four cycles of fluorouracil, epirubicin, cyclophosphamide with or without trastuzumab.[40] The study was stopped prematurely due to an interim analysis demonstrating a more than doubled pCR rate for the HER2-overexpressing patients treated with trastuzumab in addition to chemotherapy compared to chemotherapy alone.

The Taxol Epirubicin Cyclophosphamide Herceptin Neoadjuvant trial is a German non randomised phase II study that demonstrated a pCR (ypT0 ypN0) of 22.6% for 217 patients with HER2-positive breast cancer treated with epirubicin-cyclophosphamide (EC) followed by paclitaxel and trastuzumab given with paclitaxel, with a 3 years OS of 96%.[13]

The NeOAdjuvant Herceptin study, a phase III randomised trial, also tested the efficacy of trastuzumab in the NA setting.[41] It was conducted in 327 patients with locally advanced breast tumors treated with three cycles of doxorubicin-paclitaxel followed by four cycles of paclitaxel followed by three cycles of CMF. Patients with HER2-positive tumors ($n = 228$) randomized to concomitant treatment with or without trastuzumab in all chemotherapy cycles had pCR (ypT0/is ypN0) rates of 38% and 19%, respectively. The cohort of patients with HER2-negative tumors ($n = 99$) achieved a pCR rate of 16% with the same chemotherapy. Also, DFS was significantly improved in patients receiving trastuzumab, compared with those treated with chemotherapy alone.[41,42] The GeparQuattro study is a phase III trial looking into the effect of simultaneous or sequential capecitabine with docetaxel administered after EC and simultaneous trastuzumab on pCR of previously untreated stage I to stage III breast cancers.[25] 1510 patients received four cycles of EC and were randomly assigned to four cycles of docetaxel, or four cycles of docetaxel in combination with capecitabine, or four cycles of docetaxel followed by four cycles of capecitabine. Women with HER2-positive tumors ($n = 445$) received trastuzumab concomitantly with all NA chemotherapy before surgery. The pCR rate (ypT0 ypNo) in these women with HER2-positive tumors was 31.7% compared to 15.7% in the HER2-negative group ($n = 1050$).[43]

There was a comparable short-term cardiac toxicity profile, In contrast to metastatic breast disease experience,

simultaneous NA treatment with anthracyclines and trastuzumab in these trials seems to have an acceptable cardiac toxicity profile.[44]

Thus, trastuzumab became a standard treatment in the NA setting for women whit HER2 positive breast cancer, as mentioned in the current guidelines of the National Comprehensive Cancer Network that support the inclusion of trastuzumab as a standard drug in NA regimens for the treatment of Her2-positive breast cancer.

Lapatinib

Lapatinib is an oral RTK inhibitor, targeting both the Erb-B1 and Erb-B2 receptors. Pre-clinical *in vitro* and *in vivo* models indicate that lapatinib is active as monotherapy, synergistically in combination with trastuzumab, and in trastuzumab-resistant cell lines. Early clinical trials also provide evidence in patients that lapatinib is active against breast cancer.[44]

Lapatinib gained approval from the USA Food and Drug Administration (FDA) and the European Medicines Agency in 2007 after Geyer *et al*. reported positive results in heavily pretreated HER2-positive BC patients.[45]

The cardiotoxicity profile of lapatinib appears to differ from that of trastuzumab. In a pooled analysis of over 3500 patients treated with lapatinib, only 0.2% of patients developed symptomatic drop in left ventricular ejection fraction.[46]

Recent NA trials have shown that dual HER2 blockade with a chemotherapy backbone is associated with higher pCR rates than single blockade using trastuzumab alone. Four randomized trials compared efficacy of regimens that included lapatinib in comparison to trastuzumab as part of NA treatment in HER2-positive breast cancer.

In the GeparQuinto randomised phase III trial, patients with untreated HER2-positive operable or locally advanced breast cancer were randomly assigned to receive NA treatment with four cycles of EC and four cycles of docetaxel with either trastuzumab or lapatinib (1000–1250 mg/day orally) throughout all cycles before surgery.[47] The primary endpoint was pCR (defined as ypT0 and ypN0) and was analysed in all patients who received at least one cycle of EC. The pCR (ypT0 ypN0) rate in the trastuzumab arm was significantly higher than that in patients treated with lapatinib (31.3% vs. 21.7%) and the authors concluded that lapatinib should not be used outside of clinical trials as single anti-HER2-treatment in combination with NA chemotherapy.[47]

Because of the findings reporting that anti-HER2 monoclonal antibody trastuzumab and the tyrosine kinase inhibitor lapatinib had complementary mechanisms of action and synergistic antitumour activity in models of HER2-overexpressing breast cancer, the NEOALTTO study was conducted to evaluate if the two anti-HER2 agents given together would be better than single-agent therapy.[48] This phase III trial compared the efficacy of NA lapatinib plus paclitaxel versus trastuzumab plus paclitaxel versus concomitant lapatinib and trastuzumab plus paclitaxel given as NA treatment over 12 weeks in 455 patients with HER2-overexpressing primary breast cancer. The pCR was 25% and 30% with lapatinib or trastuzumab, respectively (without statistically significant differences; $P = 0.34$) and almost doubled (pCR 51%) when both agents were added to paclitaxel. All 3 treatment regimens achieved a higher pCR rate in HR-negative (34, 37, 61%, respectively) compared to HR-positive (16, 23, 46%, respectively) tumors.[49] The conclusion of this study was that dual inhibition of HER2 might be a valid approach to treatment of HER2-positive breast cancer in the NA setting. Two smaller studies have also reported comparable results.[48]

Finally these results reinforced the merit of a combined HER2 blockade and its potential and that lapatinib should not be used as single agent in the NA setting.[50]

Pertuzumab

Pertuzumab is a humanized monoclonal antibody that targets a different extracellular domain of the HER2 receptor than does trastuzumab and inhibits heterodimerization of HER2 with HER1 and especially with HER3 which is a more critical partner for HER2 pathway activation.[51]

Clinical evidence of activity of pertuzumab in combination with trastuzumab was first provided by a phase II study involving patients with HER2-positive MBC, where PR of 18% and stable disease of 27% was observed with an acceptable toxicity profile.[52]

This was the background of the CLEOPATRA study a phase III randomised trials enrolling 808 patients with HER2-positive metastatic breast cancer to receive placebo plus trastuzumab plus docetaxel or pertuzumab plus trastuzumab plus docetaxel as first-line treatment. In this trial the combination of pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel, significantly prolonged progression-free survival, with no increase in cardiac toxic effects.[5]

These findings suggest that a study of pertuzumab and trastuzumab in earlier stages of the disease is warranted. The NeoSphere study is a randomised multicentre, open-label, phase II trial testing the efficacy and safety of NA pertuzumab and trastuzumab in women with locally

advanced, inflammatory, or early HER2-positive breast cancer. In this study, 417 patients with HER2-overexpressing breast cancer were randomized to 12 weeks docetaxel plus trastuzumab, or docetaxel plus trastuzumab and pertuzumab, or trastuzumab with pertuzumab and docetaxel plus pertuzumab. pCR rates were 29, 46, 17, and 24%, respectively.[5,53]

The USA FDA granted accelerated approval to Perjeta (pertuzumab) as part of a complete treatment regimen for patients with early-stage breast cancer before surgery (NA setting) September 30, 2013.[54] These findings justify further exploration in adjuvant trials and support the NA approach for accelerating drug assessment in early breast cancer.[6] [A reminder of most relavant trials is presented in Table 2].

Trastuzumab emtansine

Trastuzumab emtansine is an antibody-drug conjugate (the cytotoxic agent (maytansinoid/emtansine) DM1 and trastuzumab are joined by a stable thioether linker).[55]

Trastuzumab alone stops growth of cancer cells by binding to the HER2/neu receptor, whereas mertansine enters cells and destroys them by binding to tubulin. Because the monoclonal antibody targets HER2, and HER2 is only over-expressed in cancer cells, the conjugate delivers the toxin specifically to tumor cells.[55,56]

Table 2 : Relevant Neoadjuvant trials with her 2 targeting agents

Trial	Number of patients	Regimen	PCR rate (%)
Neosphere[6]	417	4Xq3w D+T	29
		4Xq3w D+T+P	45,80
		4Xq3w T+P	16,80
		4Xq3w D+P	24
CHER-LOB[45]	121	12Xq1w Pac+T, 4Xq3w FEC+T	25
		12Xq1w Pac+L, 4Xq3w FEC+L	26,30
		12Xq1w Pac+T+L, 4Xq3w FEC+T+L	46,70
		12Xq1w L+T	27
NeoALTTO[49]	455	6 wT+L, 12Xq1w+Pac+T+L	51,30
		6 wT, 12Xq1w Pac+T	29,50
		6 wL, 12Xq1w Pac+L	24,70
NSABP-B41[61]	529	4XAC, 4Xq1w Pac+T	52,50
		4XAC, 4Xq1w Pac+L	53
		4XAC, 4Xq1w Pac+T+L	62
TRYPHENA[60]	225	3Xq3w FEC+T+P, 3Xq3w D+T+P	61,60
		3Xq3w FEC, 3 q3wXD+T+P	57
		6Xq3w TCH+P	66,20
GeparQuinto[48]	620	EC+T+D	30,30
		EC+L+D	22,70
TECHNO[13]	217	EC → Pac+H	38.7
Hannah[62]	596	D-FEC+T (SC)	45,50
		D-FEC+T (IV)	40,70

AC: Doxorubicin and cyclophosphamide; D: Docetaxel; FEC: Fluorouracil/epirubicin, and cyclophosphamide; L: Lapatinib; Pac: Paclitaxel; pCR: Pathologic complete response; P: Pertuzumab; T: Trastuzumab; TCH: Carboplatin, docetaxel, and trastuzumab; SC: Sub cutaneous

In the EMILIA clinical trial of women with advanced HER2-positive breast cancer who were already resistant to trastuzumab alone, it improved survival by 5.8 months compared to the combination of lapatinib and capecitabine.[57] Based on that trial, the USA FDA approved marketing on February 22, 2013.[54]

Finally, a pilot phase II study (phase II TDM4874 g [O22857; NCT01196052]) is assessing the feasibility and safety of administering TDM1 sequentially with anthracycline-based chemotherapy as adjuvant or NA therapy for patients with early-stage HER2-positive BC (NCT01196052).[58] The data reported clinical activity and favorable safety profile supporting the necessity of randomized trials.

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 TARGETED AGENTS AND CARDIAC TOXICITY

Cardiac toxicity was the predominant adverse effect identified with trastuzumab in the metastatic breast cancer clinical trials (congestive heart failure 27%).[59]

However, unlike the irreversible, dose-dependent apoptosis and necrosis of cardiomyocytes induced by anthracyclines, trastuzumab induced cardiac toxicity appears to be largely reversible.[6] Similarly, the effects of lapatinib on the myocardium appear largely reversible, not cumulative or dose related, and ultrastructural myocardial changes are not generally seen.[44] Pertuzumab has been generally well tolerated by patients enrolled in on-going clinical trials, with a low incidence of cardiac dysfunction.[51]

The potential clinical benefit of concurrent administration of anthracyclines and trastuzumab has been re-explored in the NA setting in several randomised studies with no apparent detrimental impact on cardiac health.[59]

In the TRYPHAENA trial, toxicity of three different chemotherapy schedules were evaluated: Cardiac toxicity was low (3.9–5.6%) in all arms and diarrhea was the most frequent adverse event.[60]

One should remain cautious however when considering adoption of this approach outside of the clinical trial setting, given the small numbers of highly selected patients enrolled in these studies and the short duration of follow-up.[59]

CONCLUSION

Neoadjuvant therapy in operable breast cancer demonstrated several potential benefits; Furthermore, the development of HER2-targeted therapies over the

last 30 years has been a remarkable story of basic and clinical research, advancing meaningful outcomes for both metastatic and early-stage breast cancer patients. Although the exciting prospect of potential doubling pCR with the use of combined HER2/neu blockade in the NA setting understandably demands attention, further evidence is required and caution is needed in implementing dual blockade HER2- targeted therapy for all HER2-positive in NA setting. Long-term toxicity data are needed, especially because this population is treated with curative intent and expected significant long-term survivals.

REFERENCES

1. Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, *et al.* Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: An update. J Clin Oncol 2006;24:1940-9.
2. Liu SV, Melstrom L, Yao K, Russell CA, Sener SF. Neoadjuvant therapy for breast cancer. J Surg Oncol 2010;101:283-91.
3. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: Nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr 2001;30:96-102.
4. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, *et al.* Preoperative chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008;26:778-85.
5. Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, *et al.* Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-19.
6. Gianni L, Pienkowski T, Im YH, Roman L, Tseng L-M, Liu M-C, *et al.* Neoadjuvant pertuzumab (P) and trastuzumab (H): Antitumor and safety analysis of a randomized phase II study (NeoSphere). Cancer Res 2010;70 Suppl 24. [abstract S3-2]. Available from: http://cancerres.aacrjournals.org/content/70/24_Supplement/S3-2.short [Last accessed on 2015 Feb 26]
7. Gianni L, Baselga J, Eiermann W, Porta VG, Semiglazov V, Lluch A, *et al.* Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or primary systemic therapy: European Cooperative Trial in Operable Breast Cancer. J Clin Oncol 2009;27:2474-81.
8. van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: Results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001;19:4224-37.
9. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: A meta-analysis. J Natl Cancer Inst 2005;97:188-94.
10. von Minckwitz G. Neoadjuvant chemotherapy in breast cancer-insights from the German experience. Breast Cancer 2012;19:282-8.
11. Von Minckwitz G, Loibl S, Untch M. What is the current standard of care for anti-HER2 neoadjuvant therapy in breast cancer? Oncology (Williston Park) 2012;26:20-6.
12. Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, *et al.* Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008;26:1275-81.
13. Untch M, Fasching PA, Konecny GE, Hasmüller S, Lebeau A, Kreienberg R, *et al.* Pathological complete response after neoadjuvant chemotherapy+trastuzumab treatment predicts survival and detects a patient subgroup at high need for improvement of anti – HER2 therapy. Three year median follow up data of the TECHNO trial. J Clin Oncol 2011;29:3351-7.
14. Colleoni M, Viale G, Zahrieh D, Bottiglieri L, Gelber RD, Veronesi P, *et al.* Expression of ER, PgR, HER1, HER2, and response: A study of preoperative chemotherapy. Ann Oncol 2008;19:465-72.
15. Jones RL, Lakhani SR, Ring AE, Ashley S, Walsh G, Smith IE. Pathological complete response and residual DCIS following neoadjuvant chemotherapy for breast carcinoma. Br J Cancer 2006;94:358-62.
16. Penault-Llorca F, Abrial C, Raoelfils I, Cayre A, Mouret-Reynier MA, Leheurteur M, *et al.* Comparison of the prognostic significance of Chevallier and Sataloff's pathologic classifications after neoadjuvant chemotherapy of operable breast cancer. Hum Pathol 2008;39:1221-8.
17. Guidelines of the AGO Breast Committee: Neoadjuvant (Primary) Systemic Therapy : Version 2015.1.
18. Ragaz J, Baird R, Rebbeck P, Goldie J, Coldman A, Spinelli J. Neoadjuvant (preoperative) chemotherapy for breast cancer. Cancer 1985;56:719-24.
19. Swain SM, Sorace RA, Bagley CS, Danforth DN Jr, Bader J, Wesley MN, *et al.* Neoadjuvant chemotherapy in the combined modality approach of locally advanced nonmetastatic breast cancer. Cancer Res 1987;47:3889-94.
20. Hutcheon AW, Heys SD, Sarkar TK, Aberdeen Breast Group. Neoadjuvant docetaxel in locally advanced breast cancer. Breast Cancer Res Treat 2003;79 Suppl 1:S19-24.
21. Bear HD, Anderson S, Smith RE, Geyer CE Jr, Mamounas EP, Fisher B, *et al.* Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2006;24:2019-27.
22. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, *et al.* Preoperative chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008;26:778-85.
23. Smith IC, Heys SD, Hutcheon AW, Miller ID, Payne S, Gilbert FJ, *et al.* Neoadjuvant chemotherapy in breast cancer: Significantly enhanced response with docetaxel. J Clin Oncol 2002;20:1456-66.
24. Cuppone F, Bria E, Carlini P, Milella M, Felici A, Sperduti I, *et al.* Taxanes as primary chemotherapy for early breast cancer: Meta-analysis of randomized trials. Cancer 2008;113:238-46.
25. Lee KS, Ro J, Nam BH, Lee ES, Kwon Y, Kwon HS, *et al.* A randomized phase-III trial of docetaxel/capecitabine versus doxorubicin/cyclophosphamide as primary chemotherapy for patients with stage II/III breast cancer. Breast Cancer Res Treat 2008;109:481-9.
26. von Minckwitz G, Rezai M, Loibl S, Fasching PA, Huober J, Tesch H, *et al.* Capecitabine in addition to anthracycline- and taxane-based neoadjuvant treatment in patients with primary breast cancer: Phase III GeparQuattro study. J Clin Oncol 2010;28:2015-23.
27. Zambetti M, Mansutti M, Gomez P, Lluch A, Dittrich C, Zamagni C, *et al.* Pathological complete response rates following different neoadjuvant chemotherapy regimens for operable breast cancer according to ER status, in two parallel, randomized phase II trials with an adaptive study design (ECTO II). Breast Cancer Res Treat 2012;132:843-51.
28. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177-82.
29. Sjögren S, Inganäs M, Lindgren A, Holmberg L, Bergh J. Prognostic and predictive value of c-erbB-2 overexpression in primary breast

cancer, alone and in combination with other prognostic markers. J Clin Oncol 1998;16:462-9.
30. Bargmann CI, Hung MC, Weinberg RA. The neu oncogene encodes an epidermal growth factor receptor-related protein. Nature 1986;319:226-30.
31. Coussens L, Yang-Feng TL, Liao YC, Chen E, Gray A, McGrath J, *et al.* Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. Science 1985;230:1132-9.
32. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2001;2:127-37.
33. Gschwind A, Fischer OM, Ullrich A. The discovery of receptor tyrosine kinases: Targets for cancer therapy. Nat Rev Cancer 2004;4:361-70.
34. Ménard S, Fortis S, Castiglioni F, Agresti R, Balsari A. HER2 as a prognostic factor in breast cancer. Oncology 2001;61 Suppl 2:67-72.
35. Yarden Y, Pines G. The ERBB network: At last, cancer therapy meets systems biology. Nat Rev Cancer 2012;12:553-63.
36. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-92.
37. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, *et al.* Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659-72.
38. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-84.
39. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, *et al*. BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC-T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC-TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2neu positive early breast cancer patients. Breast Cancer Res Treat 2006;100 Suppl 1:2. [Abstract 2].
40. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Isola J, *et al*. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006;354:809-20.
41. Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, *et al*. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005;23:3676-85.
42. Luca Gianni, Wolfgang Eiermann, Vladimir Semiglazov, Alexey Manikhas, Ana Lluch, Sergey Tjulandin, *et al*. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): A randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010;375:377-84.
43. Gianni L, Eiermann W, Semiglazov V, Lluch A, Tjulandin S, Zambetti M, *et al.* Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): Follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol 2014;15:640-7.
44. Untch M, Rezai M, Loibl S, Fasching PA, Huober J, Tesch H, *et al.* Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: Results from the GeparQuattro study. J Clin Oncol 2010;28:2024-31.
45. Guarneri V, Frassoldati A, Bottini A, Cagossi K, Bisagni G, Sarti S, *et al*. CHER-LOB: Preoperative chemotherapy plus trastuzumab, lapatinib or both in HER2-positive operable breast cancer--Preliminary safety report with focus on cardiac tolerability. J Clin Oncol 2011;29 Suppl. [abstract 507].
46. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, *et al*. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733-43.
47. Perez EA, Koehler M, Byrne J, Preston AJ, Rappold E, Ewer MS. Cardiac safety of lapatinib: Pooled analysis of 3689 patients enrolled in clinical trials. Mayo Clin Proc 2008;83:679-86.
48. Baselga J, Bradbury I, Eidtmann H, Di Cosimo S, Aura C, Piccart-Gebhart M, *et al*. First Results of the NeoALTTO Trial (BIG 01-06/EGF 106903): A phase III, randomized, open label, neoadjuvant study of lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2-positive primary breast cancer. Cancer Res 2010;70:82s. [abstract S3-3].
49. Untch M, Loibl S, Bischoff J, Eidtmann H, Kaufmann M, Blohmer JU *et al*. Lapatinib vs trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy: Primary efficacy endpoint analysis of the GEPARQUINTO study (GBG 44). Cancer Res 2010;70 Suppl 24. [abstract S3-1].
50. Holmes FA, Nagarwala YM, Espina VA, Liotta LA, Danso MA, Gallagher RI. Correlation of molecular effects and pathologic complete response to preoperative lapatinib and trastuzumab, separately and combined prior to neoadjuvant breast cancer chemotherapy. 2011 ASCO Annual Meeting. Abstract 506. Presented June 5, 2011.
51. Ahn ER, Vogel CL. Dual HER2-targeted approaches in HER2-positive breast cancer. Breast Cancer Res Treat 2012;131:371-83.
52. Portera CC, Walshe JM, Rosing DR, Denduluri N, Berman AW, Vatas U, *et al.* Cardiac toxicity and efficacy of trastuzumab combined with pertuzumab in patients with [corrected] human epidermal growth factor receptor 2-positive metastatic breast cancer. Clin Cancer Res 2008;14:2710-6.
53. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, *et al.* Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25-32.
54. Available from: www.fda.gov/newsevents/newsroom/pressannouncements/ucm370393.htm. [Last accessed on 2013 Sep 30]
55. Erickson HK, Park PU, Widdison WC, Kovtun YV, Garrett LM, Hoffman K, *et al.* Antibody-maytansinoid conjugates are activated in targeted cancer cells by lysosomal degradation and linker-dependent intracellular processing. Cancer Res 2006;66:4426-33.
56. Lewis Phillips GD, Li G, Dugger DL, Crocker LM, Parsons KL, Mai E, *et al.* Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res 2008;68:9280-90.
57. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, *et al.* Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783-91.
58. A Member of the Roche Group. Kadcyla [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2013.
59. Available from: https://www.clinicaltrials.gov/.[Last accessed on 2015 Jan 20]
60. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, *et al.* Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: A randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24:2278-84.
61. Robidoux A, Tang G, Rastogi P, Geyer CE Jr, Azar CA, Atkins JN, *et al*. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): An open-label, randomised phase 3 trial. Lancet Oncol 2013;14:1183-92.

62. Ismael G, Hegg R, Muehlbauer S, Heinzmann D, Lum B, Kim SB, *et al*. Subcutaneous versus intravenous administration of (neo) adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): A phase 3, open-label, multicentre, randomised trial. Lancet Oncol 2012;13:869-78.

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