What Is the Current Standard of Care for Anti-HER2 Neoadjuvant Therapy in Breast Cancer?

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This article provides a comprehensive summary of the knowledge gained from recent neoadjuvant trials conducted with agents targeting HER2, and will put them into perspective with current treatment recommendations from American and European guidelines.

Introduction

The neoadjuvant approach toward breast cancer therapy, initially developed to convert primary inoperable locally advanced tumors, is today considered a standard option, especially for patients with triple-negative or HER2-positive disease. Not only do patients with these two breast cancer subtypes have the highest frequencies of pathologic complete remission (pCR), but they also can be considered as almost cured when pCR is reached. This article will provide a comprehensive summary of the knowledge gained from recent neoadjuvant trials conducted with agents targeting HER2, and will put them into perspective with current treatment recommendations from American and European guidelines.

Which Patients With HER2-Positive Disease Are Candidates for Neoadjuvant Treatment?

Several years of neoadjuvant treatment outside clinical trials is recommended, in general, as an option for all patients for whom the indication for adjuvant chemotherapy was already given before surgery.[1,2] This recommendation is made irrespective of tumor size or nodal status, and it is based on level 1 evidence from meta-analysis of trials comparing adjuvant with neoadjuvant treatment and demonstrating similar long-term disease-free and overall survival.[3] Patients diagnosed with HER2-positive disease usually need to be treated with chemotherapy and anti–HER2-directed therapy. Neoadjuvant treatment should be withheld only in patients with tumors less than 1 cm in diameter, a size for which no evidence from prospective clinical trials supports use of trastuzumab (Herceptin) and the chemotherapy indication is uncertain.

Previously, a benefit was expected only for patients requiring mastectomy due to an unfavorable tumor–breast-size relationship, but who might be treated with breast-conserving surgery if the tumor size can be reduced.[4] This recommendation was developed at a time when pCR was a rare outcome. With recent improvement in treatment efficacy, this restriction is being revisited—especially for patients with triple-negative or HER2-positive tumors, as nowadays almost half will show a pCR. As pCR appears to be a reliable surrogate of long-term outcome in these subtypes, treatment-response information is valuable in all patients regardless of tumor size, given that a pCR can improve an initially unfavorable prognosis and the lack of a pCR might indicate the need for a more intense surveillance program or induce development of new postsurgical treatment options.

Does pCR Provide Valid Information About Long-term Outcome in Patients With HER2-Positive Disease?

Recent neoadjuvant studies support consideration of pCR as a reliable surrogate marker for long-term outcome, not only for the effect of chemotherapy but also for the effect of trastuzumab in HER2-positive breast cancer. The NOAH (Neoadjuvant Herceptin) study demonstrated that trastuzumab in addition to chemotherapy not only doubled pCR rates compared with chemotherapy alone, but it also reduced the relapse rate by half.[5] The TECHNO (Taxol Epirubicin Cyclophosphamide Herceptin Neoadjuvant) study reported a significantly more favorable disease-free and overall survival for patients who achieved a pCR compared with those who did
However, a recent pooled analysis of the German neoadjuvant studies investigated whether the prognostic impact of pCR on long-term outcome is equal to that of neoadjuvant chemotherapy and trastuzumab for patients with hormone receptor (HR)-positive and -negative tumors.[7] In fact, whereas in 298 patients with HER2-positive/HR-negative tumors, a pCR was associated with a significantly better disease-free survival compared with no pCR (hazard ratio [HR] = 8.7, P < .001), no difference in outcome was seen in 356 patients with HER2-positive/HR-positive tumors (HR = 1.2; P = .543). Even without having an explanation for this observation, information about pCR should be used with caution in these triple-positive tumors unless other data sets provide different evidence. Noninvasive disease as the only remaining tumor tissue (ypTis ypN0) after neoadjuvant chemotherapy is a rare event in HER2-negative disease, but it was reported much more frequently in patients with HER2-positive tumors treated with chemotherapy and anti-HER2 agents. In the GeparQuinto study, remaining noninvasive disease was found in 3.4% of HER2-negative patients, but in 14.3% of patients with HER2-positive disease after chemotherapy and trastuzumab.[8,9] Whereas earlier data sets, for example those from The University of Texas MD Anderson Cancer Center, could not indicate a different prognosis for 89 patients with remaining noninvasive disease and 199 patients with no remaining viable tumor cells (ypT0 ypN0),[10] a more recent pooled analysis of the German neoadjuvant studies demonstrated a significant higher relapse rate among 309 patients with noninvasive disease, compared with 955 patients with no remaining viable tumor cells.[2] In fact, the highest HR for disease-free and overall survival in patients with pCR vs without pCR was observed when using this most conservative definition. In clinical practice, therefore, one should not be overly optimistic in informing patients with remaining noninvasive disease about their prognosis.

How to Optimize pCR Rates in Patients With HER2-Positive Tumors

Adding trastuzumab

The first data on trastuzumab in the neoadjuvant setting came from a single-institution randomized study by investigators from MD Anderson Cancer Center.[11] Trastuzumab was given in combination with sequential anthracycline-taxane-based chemotherapy. An improvement in the pCR (ypT0/is ypN0) rate from 26% to 65.2% was observed at the first interim efficacy analysis, leading to an early discontinuation of the trial. Further long-term follow-up of the patients revealed a significantly lower relapse rate in patients receiving chemotherapy plus trastuzumab.

The TECHNO study reported 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 only together with paclitaxel).[6] Patients with a pCR showed a significantly better overall survival outcome than those without a pCR.

The NOAH study was conducted in 327 patients with locally advanced breast tumors treated with 3 cycles of doxorubicin/paclitaxel followed by 4 cycles of paclitaxel, and then 3 cycles of CMF (cyclophosphamide/methotrexate/fluorouracil [5-FU]).[5] 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. Again, disease-free survival was significantly improved in patients receiving trastuzumab, compared with those treated with chemotherapy alone. Despite the small number of patients, a clear trend towards a longer overall survival time was observed.

The GeparQuattro study included the largest neoadjuvant trastuzumab cohort to date.[12] Because, at the time of recruitment, it was no longer acceptable to patients and investigators to randomize trastuzumab treatment, all 445 patients with HER2-positive tumors were treated with EC and docetaxel (with or without capecitabine [Xeloda]) chemotherapy in combination with trastuzumab for 24 to 36 weeks and compared against a reference group of 1050 patients with HER2-negative tumors treated with the same chemotherapy but without trastuzumab. The pCR (ypT0 ypN0) rate was 31.7% with trastuzumab and 15.7% in the reference group.

Based on these trials, the questions of optimal duration of trastuzumab therapy before surgery and if it needs to be given simultaneously with anthracyclines remain unanswered. The TECHNO study reported a lower pCR rate with 12 weeks of trastuzumab and EC-paclitaxel (given 3-weekly) when indirectly compared with the GeparQuattro study, investigating 24 weeks of trastuzumab with EC-docetaxel. Direct evidence will come from the TRYPHAENA study, in which trastuzumab plus pertuzumab is given either during 6 cycles or only during the last 3 cycles of an FEC (5-FU-EC)-docetaxel sequence (clinicaltrials.gov No. NCT00976989).
In opposite contrast to the early experiences in metastatic breast disease, simultaneous neoadjuvant treatment with anthracyclines and trastuzumab appears to have an acceptable cardiac toxicity profile.[13] The MD Anderson investigators did not observe any chronic heart failure,[7] and only 1 of the 455 patients of the GeparQuattro study developed a persistent decrease in left ventricular ejection fraction (LVEF) below 50% during the neoadjuvant treatment phase.[6] The NOAH study measured changes in LVEF for up to 2 years following the completion of neoadjuvant trastuzumab treatment. Two patients (2%) overall developed symptomatic cardiac failure. Both responded to cardiac drugs. However, definite requirements before combining trastuzumab and anthracyclines in this setting include careful selection of patients according to pre-existing cardiac diseases and risk factors (such as a higher than normal LVEF before start of treatment), and restriction of the cumulative anthracycline dose.

Despite the high pCR rate, trastuzumab in HER2-positive patients did not result in a higher rate of breast-conserving surgery. The breast conservation rate in GeparQuattro was 63.1% and comparable to that of the reference group (64.7%).[6] In patients undergoing mastectomy, however, the residual tumor found at pathologic examination was less than 3 cm in up to 45% of patients, and in 20% of these cases a pCR was confirmed. To avoid unnecessary mastectomies, it might be necessary to establish diagnostic tools for a more reliable assessment of remaining tumor tissue.

**Including platinum compounds**

Several phase II trials have been reported to date in which the anthracycline component was substituted with carboplatin, based on preclinical data suggesting synergy between trastuzumab, a taxane, and a platinum compound.[14] A series of phase II neoadjuvant studies reported pCR (ypT0/is ypN0) rates ranging from 19% to 76%.[15-17] Since randomized comparisons of these regimens with anthracycline-taxane-trastuzumab–containing regimens are not available in the neoadjuvant setting, they should be used with caution outside of clinical trials. However, the BCIRG (Breast Cancer International Research Group) 006 study demonstrates in the adjuvant setting a slightly inferior disease-free survival for the platinum-containing regimen. GeparSixto is a recently initiated phase II study in which 300 patients with HER2-positive disease will be randomized to weekly paclitaxel/liposomal doxorubicin (Docil)/trastuzumab/lapatinib (Tykerb), with or without carboplatin. The study will provide evidence regarding the additional effect of carboplatin in this subtype of breast cancer.

**Incorporating lapatinib**

Four randomized trials compared efficacy of regimens that included lapatinib in comparison to trastuzumab as part of neoadjuvant treatment in HER2-positive breast cancer. The GeparQuinto study[3] used a 24-week sequence of EC followed by docetaxel as the chemotherapy backbone and randomized 620 patients to either trastuzumab or lapatinib given simultaneously with all cycles. The pCR (ypT0 ypN0) rate in the trastuzumab arm was significantly higher than that in patients treated with lapatinib (31.3% vs 21.7%). This difference was irrespective of HR status or extent of disease. One possible explanation for the low pCR rate in the lapatinib arm might be the lower drug exposure of patients. However, a STEPP (subpopulation treatment effect pattern plots) analysis showed no difference in pCR rates over a daily dose range of 700 to 1250 mg of lapatinib.

In parallel to the GeparQuinto study, results from the neoadjuvant NeoALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) study[18] were reported. The NeoALTTO study design was different from GeparQuinto with regard to duration of chemotherapy (12 vs 24 weeks), use of anthracycline (adjuvant vs neoadjuvant), choice of taxane (paclitaxel vs docetaxel), a window of anti-HER2 treatment without chemotherapy (yes vs no), dose of lapatinib (1500 mg/d vs 1000-1250 mg/d), and sample size per arm (≤ 154 vs ≤ 311). Whereas treatment with lapatinib–paclitaxel-lapatinib (L-PL) was associated with a trend toward a lower pCR rate (ypT0/is ypN0) compared with trastuzumab–paclitaxel-trastuzumab (H-PH), the highest pCR rate was achieved with HL-PHL. Interestingly, clinical response after 6 weeks was higher with lapatinib than with trastuzumab. The toxicity profile of the higher dose of L in combination with P in NeoALTTO appears to be different from the observations in GeparQuinto, with more grade 3/4 neutropenia and hepatic toxicity compared with H-PH and more grade 3/4 diarrhea and hepatic toxicity but less neutropenia compared with ECL-TL.

Two smaller studies have recently reported comparable results. The CHER-LOB (Chemotherapy Plus Lapatinib, Trastuzumab or Both in HER2 Positive Breast Cancer) study[19] randomized 115 patients to trastuzumab, lapatinib, or both in combination with weekly paclitaxel followed by FEC for 24
weeks. The pCR (ypT0/is ypN0) rate increased from 26% or 28% with the single agents to 43% with dual blockade. A preliminary analysis from another study of 78 patients randomized as well to T, L, or TL, with a chemotherapy backbone of FEC followed by weekly paclitaxel, revealed pCR rates of 54%, 45%, and 74%, respectively.[20] Further studies with comparable designs, conducted by Cancer and Leukemia Group B (CALGB), the European Organisation for Research and Treatment of Cancer (EORTC), and the National Surgical Adjuvant Breast and Bowel Project (NASBP) are underway.

| TABLE 1 |

Comparison of pCR (ypT0/is ypN0) Rates of Recent Neoadjuvant Trials in HER2-Positive Breast Cancer

The pCR rate (ypT0/is ypN0) of the trastuzumab-containing arm of GeparQuinto appears to be higher than the rate observed in NeoALTTO (44.0% vs 27.6%) (Table 1). Apart from potential variations in the study population, longer duration of chemotherapy and the use of anthracyclines in combination with trastuzumab might explain the higher pCR rates in GeparQuinto. The 36-week regimen used in the NOAH study[6] achieved a pCR rate of 38.0%, comparable to that seen in the GeparQuinto study. One can speculate that the dual blockade of HER2 (eg, by TL with a long duration of anthracycline-containing chemotherapy) might reach even higher pCR rates. This was indeed suggested by the small phase II trial by Holmes et al, which reported a pCR rate of 74%.[20]

**Incorporating pertuzumab**

**FIGURE 1**

Incremental Improvement in Pathologic Complete Remission (pCR) Rates by Optimizing Systemic Neoadjuvant Treatment of HER2-Positive Breast Cancer.

The first neoadjuvant study investigating pertuzumab, NeoSphere (Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation), showed that combination therapy of pertuzumab and trastuzumab with 4 cycles of docetaxel (pCR [ypT0/is ypN0/] rate, 45.8%) has at least an additive effect compared with the use of either targeted agent alone (29.0% for trastuzumab plus chemotherapy and 24.0% for pertuzumab with chemotherapy).[21] This study also included a chemotherapy-free arm, in which 12 weeks of pertuzumab plus trastuzumab yielded a pCR in 16.8% of patients. Tolerability of the antibody combination was high and cardiac toxicity in particular was low.

Another randomized phase II trial (TRYPHAENA) is exploring the two antibodies in combination with FEC followed by docetaxel in the neoadjuvant setting in preparation for an upcoming phase III adjuvant trial (Aphinity [Adjuvant Pertuzumab and Herceptin IN Initial TherapY of Breast Cancer); NCT01358877) conducted by Roche in collaboration with the Breast International Group (BIG). Figure 1 demonstrates graphically the improvement in pCR rates with the evolution of treatment for HER2-positive breast cancer over the past 15 years.

**Is There an Optimal Regimen for Patients Outside of a Clinical Trial?**
The current recommendation of the National Comprehensive Cancer Network (NCCN) guideline is to use paclitaxel plus trastuzumab followed by FEC plus trastuzumab, based on the initial small MD Anderson study.[4] The German AGO (Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe) guideline favors a sequential EC/AC followed by a taxane regimen in combination with trastuzumab, based on the GeparQuattro and GeparQuinto studies. No recommendation is given as to when to initiate treatment with trastuzumab, as a combination with anthracyclines is contraindicated in the current labeling of trastuzumab. However, Roche is seeking with the NOAH results registration for trastuzumab as neoadjuvant treatment at the European Medical Agency, which might provide the possibility of using neoadjuvant trastuzumab together with anthracyclines. A dual blockade with two anti-HER2 agents should await long-term outcome from the neoadjuvant trials as well as results from the adjuvant ALTTO study to clarify the extent to which pCRs are predictive of patient survival. Based on the trials discussed previously, this approach does not yield a higher pCR rate than a longer duration of chemotherapy and trastuzumab alone. Important questions have to be answered before lapatinib in combination with trastuzumab can be used outside of clinical trials, such as the lowest efficient dose of lapatinib, to improve tolerability, as well as patient selection. Until then, use of lapatinib in the neoadjuvant setting should be considered experimental.

Are There Factors That Can Better Select Candidates for Neoadjuvant Anti-HER2 Treatment?

| TABLE 2 |

| pCR Rates According to Hormone Receptor (HR) Status in Recent Neoadjuvant Studies Exploring Anti-HER2 Agents in Patients With HER2-Positive Breast Cancer |

A consistent observation in most of the reported studies is that patients with HR-negative tumors show higher pCR rates compared with those who have HR-positive tumors (Table 2). This might be explained by the observation that HR-positive tumors require a longer duration of neoadjuvant treatment.[22] In contrast to adjuvant trastuzumab studies, in which no such impact on survival was observed, assessment of pCR takes place before patients started on endocrine therapy.[23] Importantly, it has been shown that the estrogen receptor pathway might be a relevant escape mechanism in “triple-positive” (ie, HER2- and HR-positive) tumors.[24] A pilot trial combining trastuzumab and lapatinib with endocrine treatment reported an intriguing pCR (ypT0/is ypN0+/+) rate of 21%.[25]

Truncation of the external domain of the HER2 receptor, known as p95HER2, was postulated to be associated with resistance to trastuzumab but responsiveness to tyrosine-kinase inhibitors like lapatinib.[26] So far, results of retrospective correlation of p95HER2 with response have shown inconsistent results. In the CHER-LOB study, the pCR rate after trastuzumab or lapatinib and chemotherapy was not different for patients with p95HER2-positive or -negative tumors.[20] In the GeparQuattro study, p95HER2-positive tumors showed a significantly higher pCR rate compared with p95HER2-negative tumors (59% vs 24%), a result opposite to what was expected based on the initial hypothesis.[27]

Gene expression analysis of 114 samples from the NOAH study suggested that high expression of the plasma cell metagene and the 8q22 amplicon, and low expression of the insulin-like growth factor metagene, were associated with the increased pCR rate reported with the addition of trastuzumab to chemotherapy in HER2-positive/ER-negative tumors.[28] It appears from this study that HER2-positive/ER-positive and HER2-positive/ER-negative tumors are driven by different biologic pathways, which warrants further investigation.

Further retrospective analysis of 153 tumors from the GeparQuattro study suggested markers p4EBP1, an activator of the mammalian target of rapamycin (mTOR) pathway, or ALDH-1, a stem cell
marker, to signal resistance to trastuzumab in a multivariate regression model. In a histopathological study, ductal carcinoma in situ adjacent to invasive HER2-positive breast cancer was associated with a lower pCR rate following treatment with chemotherapy plus trastuzumab. However, all of these markers have to be validated by examination of independent cohorts and correlated with long-term patient outcome before they can be considered for clinical use, to optimally select anti-HER2 treatment in HER2-positive disease.

**REFERENCE GUIDE**

Therapeutic Agents Mentioned in This Article

- Capecitabine (Xeloda)
- Cyclophosphamide
- Docetaxel
- Doxorubicin
- Epirubicin
- Fluorouracil (5-FU)
- Lapatinib (Tykerb)
- Liposomal doxorubicin (Doxil)
- Methotrexate
- Paclitaxel
- Pertuzumab
- Trastuzumab (Herceptin)

*Drug names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products; more familiar alternative generic designations may also be included parenthetically.
How Should Treatment Be Continued After Surgery?

In almost all trials, trastuzumab treatment was completed after surgery for a total duration of 1 year, and this is currently recommended in the guidelines for treatment of HER2-positive breast cancer.[2,4] With the available knowledge regarding patient outcome in relation to pCR, a more individual approach could be envisaged, for example to stop anti-HER2 treatment in patients with a pCR or to modify anti-HER2 treatment in patients without a pCR. A reasonable approach could be to treat only those 60% of patients without a pCR with a post-surgical dual blockade. However, these approaches have to be investigated first in prospective randomized trials.

If the patient has received full sequential chemotherapy before surgery, no further chemotherapy is recommended. Local treatment should be completed by applying radiotherapy to the remaining breast, or, in the case of mastectomy, to the chest wall and regional lymph nodes, based on the initial tumor stage. Patients with HR-positive disease should be treated with endocrine therapy, similar to patients after adjuvant treatment.

Future Perspectives

Apart from investigating new anti-HER2–directed agents in this setting, simultaneous blockade of various pathways—for example, blockade of the estrogen receptor, vascular endothelial growth factor, mTOR inhibitor, or PI3Kinase inhibitors—could further improve pCR rates in HER2-positive disease and might even increase the possibility of avoiding chemotherapy in this subgroup of patients.

On the other hand, studies are required for patients with a pCR to reduce the extent of further treatment. One could even imagine that with a further enrichment of patients with a pCR, surgery might become unnecessary, as no tumor remains to be removed and the overall risk of relapse is low. Other research approaches consider omitting radiotherapy in patients who were initially node-positive but were histologically node-negative at the time of surgery, and in patients with a confirmed pCR.

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