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HER2-Orientated Therapy in Early and Metastatic Breast Cancer

Severine Iborra Elmar Stickeler

Department of Gynecology and Obstetrics, University Medical Center Aachen, Aachen, Germany

Keywords

Targeted therapy · HER2 · Early breast cancer · Metastatic breast cancer

Summary

Due to the enhanced understanding of molecular oncology and signaling pathways in breast cancer (BC), therapy management has undergone a major transformation, especially with the emergence of treatment tailored to individual disease characteristics. In the case of HER2-positive early or metastatic BC, targeted therapies are well established and remain a major focus of ongoing research. The introduction of anti-HER2 biologicals such as trastuzumab, pertuzumab, and T-DM1 has made targeted and personalized treatment possible and has clearly improved disease-free and overall survival in patients with HER2-positive BC. Moreover, neoadjuvant chemotherapy represents a well-established and often favored option for patients with operable BC and a clear indication for postoperative chemotherapy (such as HER2-positive BC). Other trials are trying to identify additional surrogate markers for therapy response and clinical outcome in the neoadjuvant setting and that way open up new perspectives with a possible de-escalation of classical treatment in favor of targeted therapy.

Introduction

Breast cancer (BC) remains the most common cancer in women worldwide. The systemic therapeutic management of BC has undergone a significant transformation during the past decade. The progress in molecular oncology and the enhanced understanding of signaling pathways have led to the emergence of targeted therapy and have made treatments tailored to individual disease characteristics possible.

The human epidermal growth factor receptor 2 (HER2) has been shown to be overexpressed in 20–30% of human BC cell lines [1]. Overexpression of HER2 in BC seems to confer a more aggressive phenotype and, historically, was associated with a poor prognosis with higher risk of recurrence, lower disease-free survival (DFS) and overall survival (OS) rates, and greater resistance to treatment [2–5]. HER2 belongs to the human epidermal growth factor receptor family consisting of 4 transmembrane tyrosine kinase receptors, namely HER1 (ErbB1), HER2 (Neu, ErbB2), HER3 (ErbB3), and HER4 (ErbB4) [2, 6, 7]. All of these receptors have a similar structure. They normally regulate cell growth and survival as well as adhesion, migration, differentiation, and other cellular responses. Ligand binding to ErbB receptors results in dimerization of 2 receptors (homodimerization if 2 identical receptors, heterodimerization if not) and activates signaling cascades. Specifically, HER2 has no known ligand and if amplified can activate other HER family members in the absence of ligands [8]. This procedure activates signaling cascades that induce cell proliferation via the Ras/MAPK (mitogen-activated protein kinases) pathway and inhibit cell death via the PI3K/Akt/mTOR (phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin) pathway [9].

HER2-Targeted Drugs

Trastuzumab

Trastuzumab, a recombinant monoclonal antibody targeting the extracellular subdomain IV of HER2, was the first biological drug approved for the treatment of HER2-positive BC and revolutionized the management of both early and advanced BC. Trastuzumab acts via different mechanisms to inhibit cell growth: prevention of HER2 dimerization, downregulation of the HER2 receptor by endo-

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Fax +49 761 4 52 07 14
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Prof. Dr. med. Elmar Stickeler
Department of Gynecology and Obstetrics
University Medical Center Aachen
Pauwelstrasse 30, 52074 Aachen, Germany
estickeler@ukaachen.de

Table 1. Overview of the different HER2-orientated therapies

Substance	Mode of action	Side effects	Indication	Regimen
Trastuzumab Herceptin®[a]	recombinant monoclonal antibody	reversible cadiotoxicity, flu-like symptoms, myelosuppression, nausea and emesis, allergy	NACT	in combination/concurrent with: a) P or D after 4×EC (AGO ++) b) P or D + pertuzumab after 4×EC (AGO +)
			adjuvant therapy	a) P or D after 4×EC (AGO ++) b) 12× P without EC if tumor < 3 cm and pN0 (AGO +) c) D and C (AGO +)
			MBC	a) D + pertuzumab (AGO ++) b) P + pertuzumab (AGO +) c) 1st-line chemotherapy d) lapatinib as 2nd-line therapy (AGO +) e) AI as 2nd-line therapy (AGO +)
Pertuzumab Perjeta®[a]	recombinant monoclonal antibody	neutropenia, diarrhea, nausea, alopecia, skin rash, peripheral neuropathy, cardiac dysfunction or failure	NACT	in combination/concurrent with: P or D + trastuzumab after 4×EC (AGO +)
			MBC	a) D + trastuzumab (AGO ++) b) P + trastuzumab (AGO +)
T-DM1 Kadcyla®[a]	antibody-drug conjugate	fatigue, anemia, nausea, hypokalemia, thrombocytopenia, increased transaminases	MBC	monotherapy: -in the 1st line if recurrence within 6 months after therapy with taxane + trastuzumab (AGO +) -in the 2nd-line (AGO ++) -in further lines (AGO ++)
Lapatinib Tyverb®[b]	dual tyrosine kinase inhibitor	skin rash (exanthema), palmar-plantar erythrodysesthesia, diarrhea, nausea, hepatotoxicity	MBC	in combination/concurrent with: -trastuzumab as 2nd- and further line therapy (AGO +) -AI as 2nd-line therapy (AGO +) -capecitabin as 2nd- and further line therapy (AGO +)

[a]Roche Pharma AG, Grenzach-Whylen, Germany.
[b]Novartis Pharma GmbH, Nuremberg, Germany.
NACT = Neoadjuvant therapy; MBC = metastatic breast cancer; D = docetaxel, P = paclitaxel; C = carboplatin; EC = epirubicin + cyclophosphamide; AI = aromatase inhibitor.

cytic destruction of the receptor, induction of cell cycle arrest, induction of antibody-dependent cellular cytotoxicity, inhibition of DNA repair, decreased angiogenesis, and impairment of constitutive HER2 extracellular domain cleavage [10, 11]. The major described side effect of trastuzumab is a reversible cardiotoxicity. Otherwise, when used alone, myelosuppression, nausea, and emesis occur in rare cases. An acute hypersensitivity-like reaction has been described in less than 10% of patients. With the significant advances in the understanding of the molecular mechanism of trastuzumab activity as well as resistance since its first approval in 1998, current research focusses on the development of new drugs to improve anti-HER2 activity and overcome resistance (table 1).

Pertuzumab

Pertuzumab is a recombinant monoclonal antibody that binds to another epitope in the extracellular domain of HER2 (subdomain II). Pertuzumab acts as a dimerization inhibitor between HER2 and the other HER family receptors by preventing the ligand-induced HER2 heterodimer, and that way provides a complementary mechanism of action to that of trastuzumab which inhibits the signaling pathway without affecting dimerization. Moreover, pertuzumab as an antibody activates the immune system, especially the natural killer cells, and therefore shows an antitumoral activity through antibody-dependent cellular cytotoxicity [12, 13]. Pertuzumab and trastuzumab synergistically block the survival of HER2-overexpressing breast cells [14]. Known toxicities of treatment with pertuzumab are neutropenia, diarrhea, nausea, alopecia, skin rash, and peripheral neuropathy. Like trastuzumab, cardiac dysfunction or heart failure have been described (table 1).

Ado-Trastuzumab Emtansine (T-DM1)

T-DM1 is an antibody-drug conjugate (ADC) consisting of the monoclonal antibody trastuzumab as a linker and the cytotoxic agent emtansine (DM1), derivative of maytansine, an antimitotic

drug. This trastuzumab conjugate simply uses HER2 as an address for the targeted delivery of a potent cytotoxic agent, emtansine, into the cell. The collateral damage to normal cells and related systemic toxicity is thus limited using treatment with ADC [15–17]. Described side effects are fatigue, anemia, nausea, hypokalemia, thrombocytopenia, and increased transaminases [15, 18] (table 1).

Lapatinib

Lapatinib is a dual tyrosine kinase inhibitor as it reversibly inhibits ErbB1 and ErbB2 tyrosine kinases. Phosphorylation and activation of cell proliferation effectors such as MAPK and Akt are subsequently blocked in ErbB1- and ErbB2-expressing tumor cell lines [19–22]. Known side effects are skin rashes (exanthema), palmar-plantar erythrodysesthesia, diarrhea, nausea, and hepatotoxicity (table 1).

HER2-Targeted Therapy in Early Breast Cancer

Neoadjuvant Therapy (NACT)

Currently, NACT represents a well-established as well as often favored option for patients with operable BC. Survival rates after NACT are comparable with those after adjuvant therapy [23, 24] since NACT contributes to surgical down-staging and thus increased rates of breast-conserving surgery. Response to NACT is currently using 2 endpoints: clinical and pathological complete response (cCR and pCR). pCR, mostly defined as no histopathological residual invasive as well as non-invasive cancer in the breast or lymph nodes after NACT, correlates strongly with the long-term outcome in this BC subtype [23, 25–27]. Various prospective, multicenter, and randomized studies have investigated the combination of trastuzumab with chemotherapy in patients with HER2-positive BC [28–30]. One of these studies, the GeparQuattro trial, a 3-arm study of the German Breast Group/Gynaecologic Oncology Study Group, assessed the effect of epirubicin (E) plus cyclophosphamide (C) followed by 1 of 3 different docetaxel-based regimens on pCR rates. In each arm, patients with HER2-positive BC received trastuzumab from the initiation of EC for 52 weeks. The pCR rate was 31.7% for patients with HER2-positive BC who received trastuzumab plus chemotherapy versus 15.7% for patients with HER2-negativ BC who received only chemotherapy ($p < 0.001$). This study demonstrated that a higher pCR rate could be expected in candidates for NACT with HER2-positive BC treated concomitantly with trastuzumab and antracycline/taxane-based chemotherapy over 24–36 weeks [28]. With the development of other HER2-targeted drugs, the evaluation of a dual blockade in the treatment of BC has become attractive. The NeoALTTO (Neo-Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) and the GeparQuinto study analyzed the combination of trastuzumab with lapatinib whereas the NeoSphere (Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation) study investigated the combination of trastuzumab and pertuzumab [31–33]. The 3-arm NeoALTTO study assessed the effect of paclitaxel plus lapatinib versus paclitaxel plus trastuzumab versus paclitaxel plus lapatinib plus trastuzumab on the pCR rate in women with operable HER2-positive BC. The pCR rate was significantly higher in the combination group (51.3%) than in the trastuzumab group (29.5%) or in the lapatinib group (24.7%) proving that dual HER2 blockade is better than single anti-HER2 therapy. The NeoALTTO study recently reported at 3.8 years of follow-up, and there was no significant difference in event-free survival between the combination arm and the trastuzumab arm [34]. NeoSphere was a 4-arm-trial (arm A: trastuzumab plus docetaxel vs. arm B: pertuzumab plus trastuzumab plus docetaxel vs. arm C: pertuzumab plus trastuzumab vs. arm D: pertuzumab plus docetaxel). Significantly improved pCR rates were found in arm B with dual inhibition of HER2 and chemotherapy (45.8%) compared to arm A with trastuzumab and docetaxel (29%) or arm D with pertuzumab and docetaxel (24%). Interestingly, arm C with only dual HER2-targeted therapy showed a low pCR rate (16.8%). The number of serious adverse events was similar in arms A, B and D, but lower in arm C [32], so that toxicity seems to not be increased with use of a triplet regimen.

Furthermore, the TRYPHAENA study, a multicenter open-label phase II trial, evaluated the cardiac tolerability of a dual blockade with trastuzumab and pertuzumab combined with anthracycline-containing or -free standard chemotherapy in the neoadjuvant treatment of operable locally advanced or inflammatory HER2-positive BC. 225 patients were randomized to 3 arms: A) FEC (5-fluorouracil, epirubicin, cyclophosphamide) for 3 cycles followed by docetaxel for 3 cycles, with trastuzumab and pertuzumab given concurrently throughout; B) FEC for 3 cycles followed by docetaxel with concurrent trastuzumab and pertuzumab for 3 cycles; and C) docetaxel plus carboplatin with concurrent trastuzumab and pertuzumab for 6 cycles. All patients then received trastuzumab to complete 1 year. Left ventricular systolic dysfunction (LVSD) was low across all arms (arm A: 5.6%, arm B: 4.0%, arm C: 2.6%). These data showed that neoadjuvant application of pertuzumab and trastuzumab, given concurrently or sequentially with an anthracycline-based chemotherapy or concurrently with a carboplatin-based chemotherapy, resulted in a low incidence of LVSD. However, cardiac function should be monitored in patients who receive adjuvant trastuzumab-based therapy. Moreover, assessment of pCR showed that all 3 therapies were highly effective, with pCR rates between 57.3 and 66.2% [35].

Adjuvant Therapy

A 2008 meta-analysis including the adjuvant trastuzumab trials HERA, NCCTG-N9831, NSABP-B31, BIRCG-006, FinHER, and PACS-04 [36] could show a mean decrease in recurrence risk of about 37% and in mortality risk of about 34%.

The 2 American trials, NCCTG-N9831 (North Central Cancer Treatment Group) and NSABP-B31 (National Surgical Adjuvant Breast and Bowel Project), had a similar design using paclitaxel either weekly or 3-weekly concurrently or sequentially with trastuzumab after 4 cycles of doxorubicin (A) and cyclophosphamide (C). The median follow-up was 8.4 years. An improvement in DFS was seen with a significant risk reduction in disease events of 40%

as well as an improvement in OS with a significant risk reduction of 37% with the combination of trastuzumab and paclitaxel after 4 cycles AC 3-weekly [37].

The HERA (HERceptin Adjuvant) trial included 5,090 patients with HER2-positive BC after completion of the locoregional therapy and a variety of adjuvant chemotherapy regimens. Patients were randomized to 1 year or 2 years of therapy with trastuzumab, or to placebo. In contrast to NCCTG-N9831 and NSABP-B31, trastuzumab was given exclusively as sequential therapy. A first analysis of the study after 1 year of follow-up showed a significant reduction in recurrence of 46% independent of the preceding chemotherapy regimen, lymph node status, or hormone receptor status, as well as a significant reduction in mortality of 44% [38]. The final analysis after a median follow-up of 8 years could not show any benefit of a 2-year therapy with trastuzumab compared to 1-year standard therapy. Moreover, in the 2-year arm, the reported rate of cardiac events was higher than in the 1-year arm. The authors concluded that 1 year of treatment provided a significant DFS and OS benefit compared with observation and should remain the standard of care [39].

The efficacy of a shortened trastuzumab application was analyzed in the FinHER and the PHARE trials. Whereas the FinHER trial could demonstrate a benefit (hazard ratio (HR) for recurrence or death in the trastuzumab group compared to the control group 0.42; $p = 0.01$) with a 9-week treatment regimen in a small cohort of patients (n = 232), the larger PHARE trial (n = 3,000) after 3.5 years of follow-up failed to show that 6 months of treatment with trastuzumab was non-inferior to 12 months of trastuzumab with regard to DFS (13 vs. 10.4%, HR 1.28) as well as OS (HR 1.47) [40, 41].

The above adjuvant trials exclusively applied polychemotherapy backbones. However, another focus was reducing cytotoxic regimes as combination partners for trastuzumab. The APT trial was a single-group multicenter study evaluating single standard treatment and included 406 patients with tumors measuring up to 3 cm and lymph node-negative, HER2-positive BC. The patients received weekly treatment with paclitaxel and trastuzumab for 12 weeks, followed by 9 months of trastuzumab monotherapy. After a 4-year median follow-up, results showed a 3-year rate of survival free from invasive disease of about 98.7%. In individual cases, monochemotherapy with weekly paclitaxel as an anthracycline-free combination partner for trastuzumab should be considered. Based on the risk/benefit ratio, considerations should be made for anthracycline-free regimens in stage I disease [42]. Another adjuvant trial, BCIRG-006 (Breast Cancer International Research Group), analyzed the effectiveness and safety of nonanthracycline-based regimen and the efficacy of trastuzumab in order to reduce cardiac toxicity. 3,222 patients were randomized in this study and treated with doxorubicin, cyclophosphamide, and docetaxel (ACT), ACT plus trastuzumab for 1 year (AC-TH), or with an anthracycline-free regimen consisting of docetaxel, carboplatin, and 52 weeks of trastuzumab (TCH). This trial confirmed the importance of trastuzumab for the treatment of HER2-positive BC showing OS and DFS benefit for both trastuzumab-containing regimes compared to ACT. Moreover, no significant difference in OS and DFS could be demonstrated between AC-TH (OS 92%, DFS 84%) and TCH (OS 91%, DFS 81%), but the TCH regimen showed lower cardiotoxicity. Especially for patients with high risk of heart failure, TCH seems to be an appropriate anthracycline-free alternative [43].

A further concern represents the dual inhibition of HER2 in adjuvant therapy. The ALTTO trial (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) randomized 8,381 patients and was the largest study analyzing the efficacy of combination therapy in the adjuvant treatment in HER2-positive BC. Women were treated after surgery and chemotherapy (anthracycline-free vs. anthracycline-based regimens) with trastuzumab (T) alone, lapatinib (L) alone, trastuzumab followed by lapatinib (T◊L), or trastuzumab and lapatinib concurrently (TL). Because of an interim analysis suggesting inferiority, the lapatinib arm was prematurely closed. The 4-year DFS in the other arms, T, T◊L and TL, was 86, 87 and 88%, respectively. Moreover, the combination of trastuzumab with lapatinib compared to trastuzumab alone did not show any benefit regarding OS, but adverse events were more likely to occur in patients treated with lapatinib [44].

Metastatic Breast Cancer Therapy

As in the adjuvant setting, treatment strategies in metastatic breast cancer (MBC) are based on tumor biology as well as clinical needs. Different parameters such as possible combination with targeted agents, previous treatments, aggressiveness of the disease, sites of metastasis, comorbidities, as well as patient preference and expectations guide the choice of treatment. In the case of MBC, monochemotherapy is preferred to polychemotherapy. One of the first studies comparing single-agent chemotherapy with or without trastuzumab was the trial by Slamon et al. [45]. Concurrent treatment with trastuzumab and first-line chemotherapy was associated with a significantly longer time to disease progression, higher response rates, longer duration of response, and improved OS. The CLEOPATRA study, a phase III trial, compared the efficacy and safety of pertuzumab, trastuzumab and docetaxel with placebo, trastuzumab and docetaxel in patients with HER2-positive first-line MBC. The dual-blockade arm showed significant benefit regarding both progression-free survival (PFS) and OS compared to the placebo arm (PFS: 12.4 vs. 18.7 months, OS: 56.5 vs. 40.8 months) [46].

Furthermore, T-DM1 is approved as a further HER2-targeted treatment in MBC, especially for patients pretreated with trastuzumab and early recurrence of the disease. The EMILIA trial, a phase III trial, evaluated the efficacy and safety of T-DM1 compared with lapatinib plus capecitabine in patients with HER2-positive locally advanced BC or MBC following prior trastuzumab-based and taxane-containing chemotherapy [47]. Whereas PFS and median OS were significantly better for the T-DM1 arm (PFS: 9.6 vs. 6.4 months, $p < 0.001$; OS: 30.9 vs. 25.1 months, $p < 0.001$), the rate of toxicities was higher in the lapatinib plus capecitabine arm. In addition, the MARIANNE study, a phase III trial, randomized 1,095 patients with first-line HER2-positive MBC treated with

T-DM1 plus placebo versus T-DM1 plus pertuzumab versus trastuzumab plus taxane-based chemotherapy (paclitaxel or docetaxel). No significant difference was shown regarding PFS in the 3 different arms [48]. Therefore, T-DM1 represents a recommended treatment alternative for patients with HER2-positive MBC in the first-line setting diagnosed less than 6 months after adjuvant therapy using taxane and trastuzumab or in the second-line treatment after trastuzumab therapy.

Summary

In the case of HER2-positive BC or MBC, targeted therapies are well established and make selective treatment possible. Based on the above studies, the breast committee of the AGO (Arbeitsgemeinschaft Gynäkologische Onkologie or German Gynaecological Oncology Group) preferred NACT as a therapeutic option in patients who have a clear indication for adjuvant postoperative chemotherapy (LoE 1/B/AGO +), especially in patient subgroups where a pCR is associated with improved survival such as HER2-positive BC (LoE 1a/A/AGO ++). Moreover, anti-HER2 treatment with trastuzumab is recommended to be given concurrently with taxane (LoE 1a/A/AGO ++) for an optimal duration of 1 year (LoE 1b/A/AGO ++) as a standard treatment for early HER2-positive BC. Trastuzumab should be administered in all HER2- and nodal-positive BC as well as nodal-negative tumors > 1 cm with an indication for chemotherapy (LoE 1a/A/AGO ++). For smaller tumors between 0.5 and 1 cm, an individual treatment decision based on additional risk factors has to be made. With regard to alternative anti-HER2 treatments, neither lapatinib nor dual therapy with lapatinib plus trastuzumab is recommended (LoE 1b/B/AGO –). In the case of HER2-positive MBC, the combination of docetaxel, trastuzumab, and pertuzumab as first-line therapy is the standard of care (LoE 1b/A/AGO ++). As second-line therapy in MBC after treatment with trastuzumab, T-DM1 is the treatment of choice (LoE 1b/A/ AGO ++).

Perspective

Further trials, such as the ADAPT study a prospective multicenter randomized study, are trying to identify additional surrogate markers for therapy response and clinical outcome in the neoadjuvant setting [49]. Recruitment for ADAPT in the subgroup of HER2- and hormone receptor-positive BC (triple-positive BC) is already finalized. This substudy, in a 3-armdesign, is comparing T-DM1 alone versus T-DM1 plus endocrine therapy versus trastuzumab plus endocrine therapy. A first analysis with 130 patients was presented at the ASCO congress in June 2015. The pCR rates in the different arms were 40.5, 45.8, and 6.7%, respectively. This data shows the strong effect of T-DM1 alone versus trastuzumab without chemotherapy. However, the additional effect of endocrine therapy is still being investigated. This information opens new perspectives for neoadjuvant therapy concepts for triple-positive BC with a possible de-escalation of classical chemotherapy in favor of targeted therapy. However, the effect on clinical outcome (OS and DFS) is not clear, and further results are to be awaited to confirm these first data.

Disclosure Statement

Both authors have no financial interest or affiliation with 1 or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this review.

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