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REVIEW ARTICLE

Current and future anti-HER2 therapy in breast cancer

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Summary

The therapeutic strategy for breast cancer with the use of targeted drugs is, at present, mainly focused on coping with HER2. Currently, lapatinib and trastuzumab are in widespread use. Virtually all completed and in progress clinical trials have demonstrated a significant enhancement in the rate of pathologic complete response (pCR), the primary endpoint in these studies, in cases of patients with HER2–positive breast cancer that received trastuzumab in the neoadjuvant setting. Use of lapatinib in the neoadjuvant setting should be considered experimental. When a 12-month course of trastuzumab was added to adjuvant chemotherapy, the disease-free survival (DFS) was greater and the overall survival (OS) was also greater. Although trastuzumab is approved as single-agent therapy, most patients are treated with trastuzumab plus cytotoxic agents. Trastuzumab, administered as single agent, produces durable objective responses and is well tolerated by women with HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. Dual targeting approach with a combination of trastuzumab and lapatinib improved progression-free survival (PFS) as compared with lapatinib alone in patients with metastatic breast cancer who have not had a response to trastuzumab. The combination of pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel, when used as first-line treatment for HER2-positive metastatic breast cancer, significantly prolonged PFS. Novel anti–HER2 targeted therapies are needed to utilise novel approaches to combat trastuzumab resistance.

Key words: adjuvant therapy, breast cancer, HER2, metastatic disease therapy, neoadjuvant therapy, novel agents

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Introduction

The therapeutic strategy for breast cancer with the use of targeted drugs is, at present, mainly focused on coping with HER2. Currently, lapatinib, a HER1 and HER2 dual inhibitor that was approved in April 2009 and trastuzumab are in widespread use. It is expected that these two drugs will be tried distinctly in clinical settings.

Human epidermal growth factor receptor 2 (HER2/*neu*) is a transmembrane tyrosine kinase [1]. The name for the HER2/*neu* protein is derived from "Human Epidermal growth factor Receptor," as it has substantial homology with the epidermal growth factor receptor (EGFR) [2]. HER2/*neu* is a protein that in humans is encoded by the *ERBB2* gene, a known proto-oncogene located at the long arm of human chromosome 17(17q21-q22) [3]. It is member of four-membered family, closely related to epidermal growth factor receptors, including epidermal growth factor receptor EGFR or HER1 (*erb*-B1), HER2 (*erb*-B2), HER3 (*erb*-B3) and HER4 (*erb*-B4) [4]. HER2 amplification or overexpression has been shown to play an important role in the pathogenesis and progression of certain aggressive types of breast cancer. Homo (HER2) or hetero (HER1, HER3, HER4) dimerisation results in the autophosphorylation of tyrosine residues within the cytoplasmic domain of the receptors [5]. Activated HER2 induces mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K/Akt), signal transducer and activator of transcription (STAT) and protein kinase C (PKC) signal transduction [6]. HER2 amplification or overexpression occur in 10-30% of breast cancers and are strongly associated with increased rate of disease recurrence and worse prognosis because such cases are more often of intermediate or high histological grade, more often lack estrogen receptors (ERs) and progesterone receptors (PgRs) (ER and PgR negative), and have lymph node metastases on presentation [7-10]. In recent years it has become an important biomarker and target of therapy for HER2-positive breast cancer [11].

HER2 testing is usually performed on biopsy samples. The HER2 status should be determined for each patient with invasive breast cancer. FDA-approved methods for HER2 testing are only ImmunoHistoChemistry (ICH) and Fluorescence *in situ* hybridization (FISH). ICH is used to measure the amount of HER2 protein present in the sample. Alternatively, FISH can be used to measure the number of copies of the gene which are present. Only IHC 3+ or FISH positive patients are candidates for anti-HER2 therapy. If a patient has an IHC 2+ result, tissue must be retested with a more precise HER2 test, the FISH test [12,13].

Researches have shown that some breast cancers that are HER2-positive can become HER2-negative over time. Likewise, a HER2-negative breast cancer can become HER2-positive over time. A biopsy of the metastatic lesion, when it is safe and easy to perform, should be considered in all patients, particularly when there is a long interval from the first diagnosis [14].

Trastuzumab is recombinant human anti-HER2 monoclonal antibody (rhuMAb-HER2) that binds to the domain IV of the extracellular segment of the HER2/*neu* receptor. This monoclonal antibody induces HER2 receptor downmodulation and, as a result, inhibits critical signalling pathways (i.e. ras-Raf-MAPK and PI3K/Akt) and blocks cell cycle progression by inducing the formation of p27/Cdk2 complexes [15]. Experiments in laboratory animals indicate that trastuzumab, when bound to a cell, induce antibody-dependent cell-mediated cytotoxicity (ADCC) [16]. Although the antitumor action of trastuzumab is not completely understood, it is thought to be mediated by several mechanisms following binding of the antibody to the extracellular domain of the HER2 receptor; these mechanisms include ADCC, inhibition of cleavage of the extracellular domain of the HER2 receptor (preventing formation of a residual truncated but constitutively active form), inhibition of ligand-independent HER2 receptor dimerization, inhibition of downstream signal transduction pathways, induction of cell-cycle arrest, induction of apoptosis, inhibition of angiogenesis, and interference with DNA repair [17]. Other potential mechanisms of action have been proposed and include downregulation of HER2 through endocytosis and trastuzumab-induced internalization of HER2 with consequent increased intracellular degradation, and potential immunological mechanisms such as elimination of tumor-specific CD4+ $CD25^{bright}$ regulatory T cells resulting in an improved immune response against HER2-positive tumors [18].

Lapatinib ditosylate is a dual tyrosine kinase inhibitor targeting both the ErbB-1 and ErbB-2 receptors [19]. Lapatinib works intracellularly and directly targets the tyrosine kinase domain. Lapatinib reversibly binds to the cytoplasmic ATP-binding site of the kinase and blocks receptor autophosphorylation and activation, thereby preventing subsequent downstream signaling events, namely simultaneous activation of extracellular signal related kinase (ERK)-1/2 and phosphatidylinositol 3' kinase (PI3K)/Akt [20]. Better central nervous system penetration was also predicted (since lapatinib is a small molecule), potentially leading to improved control of central nervous system disease by lapatinib when compared with trastuzumab [21].

Neoadjuvant setting

Neoadjuvant therapy, also known as primary systemic treatment, was initially introduced for the treatment of inoperable, locally advanced or inflammatory breast cancer [22]. Primary systemic treatment is now also considered for women with large but operable disease [23]. The rationale of this approach is to provide early chemotherapy that allows theoretical downstaging of the tumor, higher rates of breast-conserving operations and *in vivo* testing of tumor response to the chosen chemotherapy [24]. Despite the various definitions of pCR in the neoadjuvant trials, the correlation of pCR with improved DFS and OS has already been demonstrated in several studies and is currently used as a surrogate marker for chemotherapy benefit in the neoadjuvant setting [25].

The use of concurrent trastuzumab and chemotherapy in the preoperative setting has been investigated in several studies. One of the initial phase III trials randomized patients with HER2-positive, early-stage operable breast cancer to receive 4 cycles of paclitaxel every 3 weeks, followed by 4 cycles of fluorouracil + epirubicin + cyclophosphamide with or without concomitant weekly trastuzumab. Results showed significantly (p=0.016) increased the pCR rate from 26.3% in the chemotherapy-alone arm to 65.2% in the trastuzumab arm [26]. The study was closed prematurely after recruiting only 42 patients, and a third, open-label, nonrandomized cohort (n = 22) was added to the study, and all were assigned to the trastuzumab arm. Although the pCR rate was 60% (95% CI 44.3–74.3), the addition of trastuzumab to neoadjuvant therapy had a minimal effect on the rate of breast-conserving therapy performed (52.6 and 56.5% of the patients in the chemotherapy-alone and chemotherapy with trastuzumab arms, respectively). Still, one-year DFS rate (100 vs 94.7% in the chemotherapy plus trastuzumab and the chemotherapy-alone arms, respectively) and the 3-year DFS rate (100 vs 85.3%, respectively) improved significantly with the addition of trastuzumab (p = 0.041) among the randomized arms [27].

The neoadjuvant Herceptin trial (NOAH) was a large, international phase III trial designed to assess the efficacy and safety of sequential doxorubicin + paclitaxel followed by paclitaxel, then cyclophosphamide + methotrexate + 5-fluorouracil with (n=117) or without (n=118) concomitant trastuzumab, in patients with newly diagnosed locally advanced or inflammatory breast cancer. A third arm of patients (n=99) with HER2-negative disease who received the same regimen but without trastuzumab was also included. A significant improvement in the pCR rate was also observed in a subgroup analysis of patients with inflammatory breast cancer who received trastuzumab compared with those who did not (39 vs 20%; p=0.002). Also, for HER2-positive patients, the 3-year OS of the trastuzumab arm as compared with chemotherapy-alone arm was 87% (95% CI 79–92) and 79% (95% CI 70–86), respectively (p=0.114) [28].

In the Taxol-Epirubicin-Cyclophosphamide-Herceptin Neoadjuvant (TECHNO) phase II study, patients with centrally confirmed HER2-overexpressing breast cancer (≥ 2 cm or inflammatory) received four 3-week cycles of epirubicin and cyclophosphamide followed by four 3-week cycles of paclitaxel and trastuzumab before surgery. Trastuzumab was continued after surgery to complete 1 year of treatment. Thirty-nine percent of 217 enrolled patients achieved pCR. Breast conservation was possible in 64% of patients. Three-year DFS was 88% in patients with pCR compared to 73% in patients without pCR (p =0.01). Three-year OS was 96% in patients with pCR compared to 86% in patients without pCR (p =0.025) [29].

The German Breast Group/Gynecologic Oncology

Study Group (GeparQuattro) phase III study included 1,509 participants (the largest neoadjuvant trastuzumab cohort to date); 445 patients had HER2-positive tumors and were treated with trastuzumab and chemotherapy. All patients were scheduled to receive 4 cycles of epirubicin and cyclophosphamide and were then randomly assigned to 3 treatment arms: the first arm received 4 cycles of docetaxel (EC-D), the second arm received 4 cycles of docetaxel-capecitabine (EC-DX), while the third arm received 4 cycles of docetaxel followed by 4 cycles of capecitabine on days 1–14 (EC-D-X). In each arm, patients with HER2-positive disease received trastuzumab starting from the initiation of the EC for 52 weeks. Patients with HER2-negative tumors received chemotherapy only. pCR rate (defined as no invasive or *in situ* residual tumor in the breast) was 31.7%, which was 16% higher than that in the reference group (15.7%). HER2-positive patients without response to the first 4 cycles of EC showed an unexpectedly high pCR rate of 16.6% (3.3% in the reference group). This trial confirmed that combining trastuzumab with anthracycline-taxane based neoadjuvant chemotherapy resulted in a high pCR rate without clinically relevant early toxicity [30].

The GeparQuinto study used a 24-week sequence of EC followed by docetaxel as the chemotherapy backbone. Of 620 eligible patients, 309 were randomly assigned to chemotherapy with trastuzumab and 311 to chemotherapy with lapatinib. The pCR rate in the trastuzumab arm was significantly higher than that in patients treated with lapatinib (31.3 vs 21.7%). This difference was independent of hormonal receptor 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 [31].

Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO) phase 3 trial randomized women from 23 countries with HER2-positive primary breast cancer with tumors greater than 2 cm in diameter to oral lapatinib (1500 mg), i.v. trastuzumab (loading dose 4 mg/kg, subsequent doses 2 mg/kg), or lapatinib (1000 mg) plus trastuzumab. Anti-HER2 therapy alone was given for the first 6 weeks and then weekly paclitaxel (80 mg/m^2) was added to the regimen for a further 12 weeks, before definitive surgery was undertaken. After surgery, patients received adjuvant chemotherapy followed by the same targeted therapy as in the neoadjuvant phase to 52 weeks. pCR rate was significantly higher in the group given lapatinib and trastuzumab (78 of 152 patients, 51.3%; 95% CI 43—59) than in the group given trastuzumab alone (44 of 149 patients, 29.5%; 95% CI 22—37; difference 21.1%; 95% CI 9—34, p=0.0001). There was no significant difference in pCR between the lapatinib (38 of 154 patients, 24.7%; 95% CI 18—32) and the trastuzumab groups (difference −4.8%; 95% CI 3.2-8.2, p=0.34) [32].

Neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere) phase II trial randomized patients into 4 groups. Groups received 4 neoadjuvant cycles of: trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) plus docetaxel (75 mg/m^2, escalating, if tolerated, to 100 mg/m^2 every 3 weeks; group A), or pertuzumab (loading dose 840 mg, followed by 420 mg every 3 weeks) and trastuzumab plus docetaxel (group B), or pertuzumab and trastuzumab (group C), or pertuzumab plus docetaxel (group D). Group B patients had a significantly improved pCR rate (49 of 107 patients; 45.8% ; 95% CI 36—55) compared with group A patients (31 of 107; 29.0% ; 95% CI 20—38.55; p=0.0141). Twenty-three of 96 patients (24.0% ; 95% CI 15—33) in group D had a pCR, as did 18 of 107 patients (16.8%;95% CI 10—25) in group C. Patients given pertuzumab and trastuzumab plus docetaxel (group B) had a significantly improved pCR rate compared with those given trastuzumab plus docetaxel, without substantial differences in tolerability [33].

Many good quality clinical studies suggest that trastuzumab should be incorporated in the preoperative treatment of women with HER2-positive disease. The results of trastuzumab-based neoadjuvant studies have recently received significant interest in the oncology community. Virtually all completed and in progress clinical trials have demonstrated a significant improvement in the rate of pCR, the pri-

mary endpoint in these studies, in cases of patients with HER2–positive breast cancer that received trastuzumab as neoadjuvant therapy. This benefit of the addition of trastuzumab in the neoadjuvant setting appears to be independent of, if not enhanced by, the coexistence of ER positivity [34]. Among the potential explanations for the apparent greater chemosensitivity of HER2–positive tumors cotreated with trastuzumab in the neoadjuvant setting is the concept that HER2 gene amplification is in some way related to the growth and survival of breast cancer stem cells [35].

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.

Dual inhibition of HER2 might be also a valid approach to treatment of HER2-positive breast cancer in the neoadjuvant setting.

The current recommendation of the National Comprehensive Cancer Network (NCCN) guideline is to use paclitaxel followed by FEC plus trastuzumab, based on the initial small MD Anderson study [36].

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 [37].

Adjuvant setting

The selection of systemic adjuvant therapy is based on prognostic and predictive factors. Prognostic factors are measurements available at diagnosis or at the time of surgery that, in the absence of adjuvant therapy, are associated with recurrence rate, death rate, or other clinical outcome. Predictive factors are measurements associated with the degree of response to a specific therapy.

Breast cancer prognostic factors include the following: axillary lymph node status, tumor size, lymphatic/vascular invasion, patient age, histologic grade, histologic subtypes, response to neoadjuvant therapy, ER/PR status and HER2 gene amplification and/or overexpression.

Predictive factors of breast cancer include the following: ER/PR status and HER2 gene amlification and/or overexpression.

Following successful trastuzumab application in HER2-positive metastatic breast cancer it was subsequently tested for adjuvant use.

The National Surgical Adjuvant Breast and Bowel Project trial B-31 (NSABP B-31) phase III trial compared 4 cycles of doxorubicin and cyclophosphamide (AC) followed by 4 cycles of triweekly paclitaxel (arm 1- reference arm), with the same regimen plus 52 weeks of 3-weekly trastuzumab beginning on day 1 of the triweekly paclitaxel (arm 2) [38]. The North Central Cancer Treatment Group trial N9831 (NCCTG N9831) compared 4 cycles of AC followed by 12 weeks of weekly paclitaxel (arm A - reference arm), with the same regimen plus 52 weeks of 3-weekly trastuzumab either following weekly paclitaxel (arm B), or beginning on day 1 of weekly paclitaxel (arm C). Joint analysis of data from NCCTG N9831 and NSABP B-31, after a median follow-up of 3.9 years, showed a continuing highly statistically significant reduction in DFS in favor of the trastuzumab-containing arm ($p<0.001$). Similarly, a continuing statistically significant reduction in death rate (39%) in favor of the trastuzumab-containing arm ($p<0.001$) was registered [39].

The Breast Cancer International Research Group 006 (BCIRG 006) phase III randomized trial compared 4 cycles of doxorubicin and cyclophosphamide followed by 4 cycles of triweekly docetaxel (reference arm) with same regimen plus 52 weeks of trastuzumab, weekly at the docetaxel phase and triweekly thereafter, beginning on day 1 of triweekly docetaxel. This trial is distinguished from the others by the involvement of a nonanthracycline regimen, consisting of docetaxel, carboplatin and trastuzumab, with the aim of reducing cardiotoxicity [40]. At a median follow-up of 5.4 years, women in both groups receiving trastuzumab had better 5-year DFS rates (84% for doxorubicin and cyclophosphamide followed by docetaxel plus trastuzumab and 81% for docetaxel, carboplatin and trastuzumab) than women who received doxorubicin and cyclophosphamide-trastuzumab alone (75%). The differences for both trastuzumab-containing regimens were statistically significant [41].

The Herceptin Adjuvant (HERA) phase III study differed from the other trials in that patients were randomized at the point of completion locoregional therapy and at least 4 cycles of neoadjuvant or adjuvant chemotherapy to either observation alone, to one year of triweekly trastuzumab, or two years of triweekly trastuzumab. Adjuvant endocrine therapy, primarily 20 mg of tamoxifen per day, was given after chemotherapy to women with ER- or PgR-positive disease. An amendment to the protocol allowed aromatase inhibitors to be used instead of or in sequence with tamoxifen. Data were available for 1694 women randomly assigned to two years of treatment with trastuzumab, 1694 women assigned to one year of trastuzumab, and 1693 women assigned to observation. Results only of treatment with trastuzumab for one year or observation showed an unadjusted hazard ratio (HR) for an event in the trastuzumab group, as compared with the observation group of 0.54 (95% CI 0.43-0.67; p<0.0001). Treatment with adjuvant trastuzumab for 1 year after chemotherapy was associated with significant clinical benefit at 4-year median follow-up [42]. The substantial selective crossover of patients in the observation group to trastuzumab was associated with improved outcomes for this cohort [43].

The Finland Herceptin (FinHER) phase III trial enrolled 1010 women with axillary node–positive or high-risk node-negative breast cancer. The patients were randomly assigned to receive 3 cycles of docetaxel or vinorelbine, followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide in both groups. Women with HER2-positive cancer (n=232) were further assigned to either receive or not trastuzumab for 9 weeks with docetaxel or vinorelbine [44]. The median follow-up time was 62 months after random assignment. The filnal results showed that women assigned to docetaxel had better distant DFS than those assigned to vinorelbine (HR -0.66; 95% CI 0.49-0.91; p=0.010). In the subgroup of HER2-positive disease, patients treated with trastuzumab tended to have better distant DFS than those treated with chemotherapy alone (HR -0.65; 95% CI 0.38-1.12; p=0.12; with adjustment for presence of axillary nodal metastases, HR - 0.57; p=0.047). In exploratory analyses, docetaxel, trastuzumab, and fluorouracil, epirubicin, and cyclophosphamide improved distant DFS compared with docetaxel plus fluorouracil, epirubicin, and cyclophosphamide (HR-0.32; p=0.029) and vinorelbine, trastuzumab, and fluorouracil, epirubicin, and cyclophosphamide (HR-0.31; p=0.020). The authors concluded that adjuvant treatment with docetaxel improved distant DFS compared with vinorelbine. A brief course of trastuzumab administered concomitantly with docetaxel was safe and effective and warrants further evaluation [45].

In the Programmes d'Actions Concertées Sein (PACS) 04 PHASE III trial 3010 patients with operable node-positive breast cancer were randomly assigned to receive adjuvant anthracycline-based chemotherapy with or without docetaxel. Patients who presented HER2-overexpressing tumors were further randomly assigned to either a sequential regimen of trastuzumab (6 mg/kg every 3 weeks) for 1 year or observation. The primary end point was DFS. At the date of analysis, October 2007, 129 DFS events were recorded. Random assignment to the trastuzumab arm was associated with a nonsignificant 14% reduction in the risk of relapse (HR-0.86; 95% CI 0.61-1.22; p=0.41). Three-year DFS rates were 78% (95% CI 72.3-82.5) and 81% (95% CI 75.3-85.4) in the observation and trastuzumab arms, respectively. After a 47-month median follow-up, 1 year of trastuzumab given sequentially after adjuvant chemotherapy was not associated with a statistically significant decrease in the risk of relapse [46].

Two major adjuvant trials of lapatinib in the adjuvant setting, TEACh and ALTO, are now ongoing.

The TEACH trial (Tykerb Evaluation After CHemotherapy; EGF105485) is a phase III, randomised, double-blind, placebo-controlled, study of lapatinib vs placebo in women with HER2-positive breast cancer who have not been previously treated with trastuzumab. Eligible women must have completed adjuvant chemotherapy and be free of disease. The median time from diagnosis to study entry was 3 years. The aim of this phase III trial is to determine whether lapatinib, given for 1 year, will improve DFS in women with early HER2 overexpressing breast carcinoma. More than 3000 women who completed neoadjuvant or adjuvant chemotherapy, did not receive trastuzumab and did not have evidence of disease were randomised to re-

ceive lapatinib or placebo for up to 12 months or until a DFS event, defined as objective disease recurrence, a second primary cancer, contralateral breast cancer or death from any cause [47]. After a median follow up of 4 years, DFS events occurred in 13% of the patients in the lapatinib arm and 17% of the patients in the placebo arm of the trial (HR- 0.83; 95% CI 0.70-1.00; p=0.053). Therefore, although an improvement in DFS in favor of lapatinib was observed, this result did not meet the prespecified criteria for statistical significance [48].

The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) is a large, randomized phase III trial. The rationale for the ALTTO trial is: a) the potential development of resistance during or after adjuvant trastuzumab therapy; b) the inability of the monoclonal antibody to cross the blood-brain barrier under physiological circumstances; and c) concerns about the cardiac safety of trastuzumab [49]. In the ALTTO trial, patients with centrally determined early-stage HER2-overexpressing breast cancer are randomized to single-agent trastuzumab or lapatinib or the combination of both drugs for 1 year. In a fourth study arm, patients are treated with trastuzumab for 3 months, followed by lapatinib for 7.5 months after a 6-week wash-out period [50]. ALTTO has randomised 8381 patients at nearly 1,500 research sites in 44 countries. Patient enrolment began in June 2007 and completed in July 2011. On August 18, 2011, the ALTTO Independent Data Monitoring Committee (IDMC) met to review the first planned interim analysis. The IDMC reported that the comparison of lapatinib-alone vs trastuzumab-alone crossed the futility boundary, indicating that the lapatinib-alone arm was unlikely to meet the prespecified criteria to demonstrate non-inferiority to trastuzumab-alone with respect to DFS. The IDMC also stated that the other three arms (trastuzumab alone, sequential trastuzumab/lapatinib arm and the combination arm) should continue as planned with no changes. The results will provide answers about the role of lapatinib in the adjuvant treatment for HER2-positive breast cancer.

The major phase III trastuzumab-based adjuvant trials mentioned above used a variety of cytotoxic agents in various combinations, doses, and order of administration. When a 12-month course of trastuzumab was added to adjuvant chemotherapy, the DFS was 33–52% higher and the OS was 34–41% higher. The improvement in DFS was independent of age, nodal status, hormonal status, or tumor size in all trials. As the results of longer treatment duration are awaited, one-year trastuzumab should be considered the current standard, because this was the duration used in the majority of the randomized trials. It is very likely that trastuzumab is more active when given concurrently with than sequentially after chemotherapy as long as the same chemotherapy regimen is employed, according to the joint analysis of the NCCTG N9831 and NSABP B31 trials.

The adjuvant lapatinib, as monotherapy, did not meet the prespecified criteria for statistical significance in the TEACH trial, so it is not recommended as adjuvant therapy.

The superiority of lapatinib and trastuzumab combination to either therapy alone in the adjuvant setting remains to be revealed in the ALTTO study.

Metastatic disease setting

Despite the practice-changing impact of trastuzumab and the substantial improvement in outcomes, patients with HER2-positive metastatic breast cancer ultimately die of their disease.

Trastuzumab therapy was initially designed only for patients with advanced/relapsed breast cancer that overexpressed HER2 protein [51]. Since its launch in 1998, trastuzumab has become an important therapeutic option for patients with HER2–positive breast cancer and is widely used in metastatic settings [52]. Although trastuzumab is approved as a single-agent regimen, most patients are treated with trastuzumab plus cytotoxic agents.

In the pivotal phase III trial [57] of trastuzumab in combination with chemotherapy for patients with metastatic disease, of 469 patients who were enrolled, 235 were randomized to trastuzumab plus chemotherapy and 234 were randomized to receive chemotherapy alone. The survival data showed that at one year after treatment, 67% of the chemotherapy-alone patients were alive vs 78% of patients who had received chemotherapy plus trastuzumab. Updated in April 1999, 36% of the patients were alive in the chemotherapy-alone

arm vs almost 50% when chemotherapy was combined with trastuzumab. These results were achieved despite the fact that women who were randomized to the chemotherapy-alone arm at the time of progression were permitted to subsequently receive trastuzumab. Of the 65% who elected this option, one third responded. The median survival of the population who received trastuzumab plus chemotherapy was lengthened by a factor of almost 25% [54].

One of the first studies that used trastuzumab in women that has progressed after chemotherapy for metastatic disease enrolled 222 women with HER2-overexpressing metastatic breast cancer that had progressed after one or two chemotherapy regimens. The patients received an i.v. trastuzumab loading dose of 4 mg/kg followed by a 2 mg/kg maintenance dose at weekly intervals. The study patients had advanced metastatic disease and had received extensive prior therapy. A blinded, independent response evaluation committee identified 8 complete and 26 partial responses, for an objective response rate of 15% in the intent-to-treat population (95% CI 11-21). The median duration of response was 9.1 months and the median duration of overall survival was 13 months. The median time to treatment failure among the 34 patients with a response was 11 months (range 2 to >28 months). In contrast, compared to prior chemotherapy regimens, the median time to treatment failure was 5.4 months (range 0-27.4 months) [55].

In a multi-institutional study, which was conducted at 18 centers in the United States (n=17) and Canada (n=1), the investigators enrolled 114 patients who had HER2 overexpression (2+ or 3+) and had not previously received cytotoxic chemotherapy for their metastatic breast cancer to receive trastuzumab. In the intent-to-treat analysis of all enrolled patients, there were 7 complete and 23 partial responses, for an objective response rate of 26% (95% CI 18.2-34.4). An additional 13 patients had a minor response or stable disease for longer than 6 months for a clinical benefit (complete response + partial response + minor response + stable disease > 6 months) rate of 38% (95% CI 28.8-46.9). Three patients were not assessable because of lack of metastatic breast cancer. One patient requested study removal after one dose of trastuzumab, and another one requested study removal after 4 doses and no post-baseline tumor evaluation. In assessable patients, there were 7 complete and 22 partial responses for an objective response rate of 26% (95% CI 18.0-34.3). Responses also occurred in patients with hormone receptor–positive and hormone receptor–negative tumors, lung or liver metastases, disease-free interval of 12 months or less and more than 12 months, and previous adjuvant doxorubicin. However, responses were seen only in patients whose tumors overexpressed HER2 at the 3+ level and not at the 2+ level [56].

A pivotal phase-III trial [57] evaluated the combination of lapatinib (1250 mg daily) plus capecitabine (2000 mg/ m^2 daily, given on days 1–14 of a 21-day cycle) vs capecitabine alone in patients with HER2-positive, locally advanced or metastatic breast cancer who were refractory to either an anthracycline, or taxane and trastuzumab. In this trial of 324 patients, lapatinib plus capecitabine resulted in a 4-month improvement in median time to progression (8.4 vs 4.4 months; HR=0.49; p<0.001). A higher response rate also favored the combination arm (22 vs 14%), although this was not statistically significant. In the updated efficacy analyses, the improvement in median time to progression was confirmed (6.2 vs 4.3 months; HR=0.57; p=0.00013), although no statistical differences in OS were demonstrated [58,59].

The {"type":"entrez-protein","attrs":{"term_id":"327544443","text":"EGF30008"}}EGF30008 trial was a phase III trial that evaluated letrozole plus lapatinib (n=642) vs letrozole plus placebo (n=644) in treatment-naive postmenopausal patients with hormone receptor-positive metastatic breast cancer. Among the 219 ER-positive, HER2-positive patients, a 5.2-month improvement in the primary endpoint of median PFS was seen in the lapatinib/letrozole arm (8.2 vs 3.0 months; HR=0.71; p=0.019). OS data are awaited [60]. Interestingly, a biomarker analysis of this study suggested that there may be a role for HER-family targeting with letrozole in HER2-negative, ER low-expressing tumors [61].

In the {"type":"entrez-protein","attrs":{"term_id":"327544415","text":"EGF30001"}}EGF30001 phase III trial, which evaluated lapatinib plus paclitaxel vs paclitaxel alone in the first-line setting, a median time to progression improvement of 11.3 weeks was observed in the HER2-positive population (36.4 vs 25.1 weeks;

HR=0.53), albeit on a subset analysis [62,63].

Total HER2 blockade with lapatinib and trastuzumab was also evaluated in a phase III trial of lapatinib plus trastuzumab vs lapatinib alone in patients with metastatic breast cancer who had received a median of 3 prior trastuzumab-containing regimens. An almost 4-week improvement in PFS (12.0 vs 8.1 weeks; HR=0.73; p=0.008), as well as a doubling of the clinical benefit ratio (24.7 vs 12.4% p=0.01) were observed [64].

The TBCRC 003 phase II trial evaluating the combination of lapatinib and trastuzumab in patients with HER2-positive metastatic breast cancer [cohort 1 (n=40): no prior lapatinib, trastuzumab or chemotherapy for metastatic disease and >1 year since adjuvant trastuzumab, if received; cohort 2 (n=47): 1 to 2 prior lines of chemotherapy, including trastuzumab, or relapse within 1 year of adjuvant trastuzumab]. Interim results were recently presented and showed objective response rates of 41.7 and 25% in cohorts 1 and 2, respectively [65].

Trastuzumab, administered as a single agent, produces durable objective responses and is well tolerated by women with HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease.Significant advances in molecular-targeted therapies have provided more effective and less aggressive forms of therapy for patients with HER2-overexpressing metastatic breast cancers. Specific recommendations for the optimal treatment of HER2-overexpressing metastatic disease are challenging because considerable advances in the field have been made. At the time of disease progression, clinicians frequently continue trastuzumab but change to an alternative chemotherapy agent. Dual targeting approach with a combination of trastuzumab and lapatinib improved PFS as compared with lapatinib alone in patients with metastatic breast cancer who have not had a response to trastuzumab. Any of these therapeutic approaches would be considered to be appropriate for a patient with progressive disease, but there is not one approach that is convincingly superior to another, and these options can be used in sequence The clinical dogma is to leverage the HER2 status of the tumor and continue anti-HER2 therapy, in some form, indefinitely. Although these strategies can confer benefit to some patients after disease progression, none of these strategies are curative.

Very promising results of dual blockade were presented in the CLEOPATRA phase III trial in which 808 patients with HER2-positive metastatic breast cancer were randomly assigned to receive placebo plus trastuzumab plus docetaxel (control group) or pertuzumab plus trastuzumab plus docetaxel (pertuzumab group) as first-line treatment until the time of disease progression or the development of toxic effects that could not be effectively managed. The primary end point was independently assessed PFS. Secondary end points included OS, PFS as assessed by the investigator, the objective response rate, and safety. The median PFS was 12.4 months in the control group, as compared with 18.5 months in the pertuzumab group (HR for progression or death 0.62; 95% CI 0.51-0.75; p<0.001). The interim analysis of OS showed a strong trend in favor of pertuzumab plus trastuzumab plus docetaxel. The safety profile was generally similar in the two groups, with no increase in left ventricular systolic dysfunction; the rates of febrile neutropenia and diarrhea of grade 3 or above were higher in the pertuzumab group than in the control group. The combination of pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel, when used as first-line treatment for HER2-positive metastatic breast cancer, significantly prolonged PFS, with no increase in cardiac toxic effects [66].

There is no doubt that trastuzumab has provided significant clinical benefit in patients with HER2-positive breast cancer. Still, primary (*de novo*) and secondary (acquired) resistance represents a real clinical challenge. Lapatinib has demonstrated modest clinical activity in this setting and highlights the importance of ongoing HER2 blockade in trastuzumab-refractory states. Novel anti-HER2 targeted therapies are needed to utilise novel approaches to combat trastuzumab resistance.

Novel anti-HER2 targeted therapies

Pertuzumab is an anti–HER1/HER2 monoclonal antibody that inhibits HER1–HER2 dimerization. Pertuzumab does cause an ADCC reaction, but it does not block HER2 shedding. Pertuzumab may have efficacy in breast cancers with low levels of HER2 overexpression or in cases in which HER2 protein levels are normal but HER1

(EGFR) levels are elevated [67]. Clinical trials evaluating pertuzumab efficacy in metastatic breast cancer have been successful to date [66].

Ertumaxomab is a trifunctional bispecific antibody targeting HER2 on tumor cells and CD3 on T cells that has the capability to redirect T cells, macrophages, dendritic cells, and natural killer cells to the sites of tumor metastases [68]. In a phase I trial, ertumaxomab treatment was associated with one complete response and several partial responses in heavily pretreated patients with metastatic breast cancer [69].

MDX-H210MDX-H210, a bispecific monoclonal antibody targeting HER2 combined with G-CSF has been tested in early clinical trials with limited clinical response to date [70,71].

Trastuzumab was conjugated with the fungal toxin maytansine (DM-1) [72]. Phase II trials of this agent are currently in progress and a recent interim analysis showed 40% response rate in a heavily pretreated patient cohort including prior trastuzumab and/or lapatinib therapy [73].

A number of tyrosine kinase inhibitors (TKIs) are in early-stage clinical development for the treatment of HER2–positive breast cancer. Similar to lapatinib, neratinib (HKI-272) - a HER1/HER2 dual kinase inhibitor - recently was shown to exert efficacy and acceptable toxicity in an early-stage clinical trial for advanced metastatic breast cancer [74]. A number of additional HER1/HER2 TKIs, pan-HER TKIs, and dual HER2/VEGF TKIs are in various stages of preclinical and early clinical development.

Meanwhile, anti-VEGF strategies, such as bevacizumab, have demonstrated promising activity and phase III results are eagerly awaited. Other investigational agents in HER2-positive metastatic breast cancer, including hsp90 and mTOR inhibitors, utilise novel approaches to combat trastuzumab resistance and have also shown promising activity in early-phase clinical trials.

Finally, ongoing translational research is critical in the development of novel biomarkers predictive of clinical benefit with these evolving targeted agents in HER2 positive breast cancer in order to minimize drug-related toxicities and to ultimately improve patient outcomes.

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