Targeted therapy in HER2-positive breast cancer (Review)

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Abstract. Treatment options for breast cancer vary based on tumor surface markers and clinical factors, including cytotoxic chemotherapy, hormonal therapy, biological therapy or a combination thereof. An important molecular determinant of therapy is the human epidermal growth factor receptor 2 (HER2) positivity of the tumor, which has been identified in 20-25% of breast cancers and is a prognostic marker of poor outcome. The advent of HER2-targeted therapies has significantly improved the survival of patients with HER2-positive breast cancer. This review focuses on current HER2-targeted therapeutic options for patients with HER2-positive breast cancer, including monoclonal antibodies and tyrosine kinase inhibitors (TKIs).

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1. Introduction

Breast cancer is the most frequently diagnosed cancer and one of the major causes of mortality in females worldwide. Breast cancer is also one of the most investigated diseases and its management has progressed rapidly into the molecular era. The current therapies have merged clinical, pathological and molecular understanding to improve outcomes, resulting in a decrease in mortality.

One of the major challenges in breast cancer treatment stems from the fact that it is a heterogeneous disease comprising at least five subtypes (1). It has become evident that 20-25% of breast cancers are classified as human epidermal growth factor receptor 2 (HER2)-positive, which denotes an aggressive phenotype resulting in reduced disease-free and overall survival compared with other breast cancer subtypes (2,3). HER2 belongs to the human epidermal growth factor receptor (EGFR) family, which includes the closely related receptors HER1 (or EGFR), HER2, HER3 and HER4, also known as the HER family. HER receptors are transmembrane glycoproteins containing an extracellular ligand-binding domain and an intracellular receptor tyrosine kinase (TK) domain, bothe of which are important in tumor development via their effect on cell proliferation, migration, angiogenesis and anti-apoptosis (4). Although the subtypes of HER receptors have distinct extracellular ligand-binding domains, they share a similar TK domain (5). Ligand binding results in receptor homo- or hetero-dimerization. HER2 has no known ligand and is activated through the heterotypic interaction of its extracellular domain (ECD) with that of other EGFR receptors (6). It is also the preferred dimerization partner within the EGFR family (7). Within dimers, the interactions between the intracellular domains of the receptors lead to autophosphorylation of the tyrosine kinase, allowing for subsequent signal transduction which is associated with cell proliferation, apoptosis, angiogenesis and metastasis (4). In addition to being a reliable biomarker, HER2 is a validated therapeutic target. Treatment specifically targeted at HER2 has dramatically improved survival during the past decade in patients with HER2-positive breast cancer. This review focuses on current treatments for patients with HER2-positive breast cancer, including monoclonal antibodies and TK inhibitors (TKIs) which have markedly improved the natural history of HER2-positive breast cancer.

2. Monoclonal antibodies

Trastuzumab. Trastuzumab (Herceptin; Genentech/Roche, South San Francisco, CA, USA), the first available HER2-targeted therapy, is a humanized murine IgG monoclonal antibody that binds to the HER2 ECD. Its antitumor activity has not been completely ascertained, however, it is thought to result from a combination of antibody-dependent cell-mediated cytotoxicity, inhibition of cleavage of the ECD of the HER2 (8), decreased DNA repair, decreased intracellular signal transduction and

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anti-angiogenic effects (9,10). Trastuzumab-based treatment strategy has established a milestone in the therapy of HER2-positive breast cancer with attractive clinical benefits in the treatment of metastatic breast cancer, as well as adjuvant chemotherapy and neoadjuvant chemotherapy.

Adding trastuzumab to chemotherapy in the first-line treatment of HER2-positive metastatic breast cancer (MBC) was based on the pivotal phase III trial in which 469 women with HER2-positive MBC were randomized to receive standard chemotherapy (paclitaxel or anthracycline/cyclophosphamide) with or without trastuzumab. The combination improved response rates (RRs; 50 vs. 32%), extended time to progression (TTP; 7.4 vs. 4.6 months) and median overall survival (OS; 25 vs. 20 months) (11). Subsequently, results of two randomized trials demonstrated the benefit of adding trastuzumab to chemotherapy in the treatment of HER2-positive MBC, as well as significant improvements in TTP and OS (12,13). Besides paclitaxel and docetaxel, other combination regimens of trastuzumab with chemotherapy drugs such as vinorelbine, capecitabine, platinum salts and gemcitabine, have also shown clinical benefit in patients with HER2-positive MBC (14-18). Single agent trastuzumab has also been evaluated, however, it yielded lower RRs compared with the combination of chemotherapy and trastuzumab (19). Thus, it seems appropriate to prescribe trastuzumab monotherapy for elderly or frail patients whose performance status permits administration of trastuzumab but not chemotherapy.

In the phase III TAnDEM post-menopausal patients with HER2-positive, oestrogen receptor (ER) + MBC were randomized into the primary therapy with anastrozole alone group or the anastrozole combined with trastuzumab. Results of that study showed that the addition of trastuzumab significantly improved RRs (20.3 vs. 6.8%) and progression-free survival (PFS; 4.8 vs. 2.4 months) (20). Therefore, blockade of the downstream signaling pathway of the HER2 receptor might enhance endocrine sensitivity of HER2-positive, ER^+ breast cancer cells.

Trastuzumab has a marked effect on HER2-positive MBC, however, progression remains unavoidable. The synergy between trastuzumab and a variety of chemotherapeutic agents is not only exploited in first-line setting but also beyond disease progression in pretreated patients. Data from retrospective and prospective clinical studies suggest that continuation of trastuzumab with second- and third-line chemotherapeutic agents following disease progression on previous administration of trastuzumab is capable of eliciting objective responses and delaying disease progression (21-23). The Trastuzumab Beyond Progression study randomly assigned 156 patients who had progressed from trastuzumab to capecitabine with trastuzumab or capecitabine alone. Continuation of trastuzumab with capecitabine resulted in a significantly improved TTP (8.2 vs. 5.6 months) and RR (48.1 vs. 27.0%) as compared with capecitabine alone (23). In the clinic, continued use of trastuzumab has been a therapeutic option for patients who progress during or after treatment with trastuzumab-containing treatment regimens.

After its approval in the metastatic setting, trastuzumab was evaluated in the adjuvant setting in several large prospective randomized trials. Results of a recent meta-analysis of published prospective randomized trials that included over 13,000 patients demonstrated that the combination of trastuzumab with adjuvant chemotherapy produced a significant benefit in disease-free survival (DFS) odds ratio (OR)=0.69, OS (OR=0.78), locoregional recurrence (OR=0.53) and distant recurrence (OR=0.62), as compared with chemotherapy alone (24). Outcome was significantly improved with trastuzumab as monotherapy following the completion of chemotherapy, and in combination with paclitaxel or docetaxel following the completion of doxorubicin plus cyclophosphamide, or given concurrently with carboplatin and docetaxel. Based on these results, adjuvant treatment of early-stage breast cancer with combined trastuzumab and chemotherapy has become standard in patients with HER2-positive tumors >1 cm in size or positive lymph nodes. Few patients with HER2-positive tumors, a diameter of ≤1 cm and negative lymph nodes were included in the majority of randomized trials, suggesting that exhaustive data on trastuzumab for small node-negative tumors are lacking. Current data suggest that node-negative HER2-positive tumors of 0.6-1.0 cm are thought to benefit from adjuvant trastuzumab therapy, based on the evidence for an inferior clinical outcome in these patients (25). Two ongoing trials that include patients with small HER2-positive, node-negative breast tumors may explore less toxic chemotherapy and/or short-course trastuzumab. Currently, treatment with trastuzumab for 1 year in addition to chemotherapy is the only approved HER2-specific adjuvant treatment for patients with HER2-positive early breast cancer. Several trials have addressed the optimal duration of trastuzumab on adjuvant therapy. Recently, data from the HERA study, which is the only randomized trial investigating whether a longer duration of trastuzumab further improves efficacy outcome, suggested that OS in the 2-year and 1-year arm of trastuzumab was comparable [hazard ratio 1.05, 95% confidence interval (CI), 0.86-1.28; p=0.63], but the cardiotoxicity was higher in the 2-year arm (7.2 vs. 4.1%). These results confirm that 1 year of adjuvant trastuzumab remains the standard of care for HER2-positive early breast cancer and the significant improvement in DFS and OS for trastuzumab persists at a median follow-up of 8 years (26). Findings of the NCCTG N9831 trial suggest that trastuzumab is more effective when initiated concurrently with the taxane component of adjuvant chemotherapy compared with initiation after completion of chemotherapy (27). This approach also reduces the duration of intravenous therapy by approximately 3 months, which might improve convenience (28).

Benefits from use of trastuzumab in HER2-positive early and MBC have been noted. However, the addition of trastuzumab to neoadjuvant treatment in the locally advanced setting is also attractive. Initial data on trastuzumab in the neoadjuvant setting revealed that the pathologic complete response (pCR) rate, which is connected with a significantly improved outcome, increased from 26.0 to 65.2% with the addition of trastuzumab to sequential anthracycline- and taxane-based chemotherapy and long-term follow-up of the patients revealed a significantly lower relapse rate in patients receiving chemotherapy plus trastuzumab (29). Subsequently, several randomized trials evaluating the efficacy of a wide variety of trastuzumab-containing regimens in the neoadjuvant setting have been reported. A meta-analysis of randomized trials indicated that the addition of trastuzumab to neoad-

juvant chemotherapy significantly improves pCR rates and event-free survival in patients with locally advanced breast cancer compared with chemotherapy alone (30). Therefore, the addition of trastuzumab to neoadjuvant chemotherapy in HER2-positive breast cancer is considered a standard option. In almost all trials, trastuzumab treatment was completed after surgery for a total duration of 1 year and this is currently recommended in the NCCN Clinical Practice guidelines (31).

In a large clinical trial, it was reported that trastuzumab is generally well tolerated despite an association with potential cardiotoxicity (32). Trastuzumab-related cardiac dysfunction, which involves asymptomatic decrease in the left ventricular ejection fraction (LVEF), may be influenced by concurrent or sequential chemotherapy as well as type of chemotherapy. A retrospective review of records for patients with MBC revealed that the highest incidence of cardiac dysfunction was observed with the concurrent use of trastuzumab and anthracycline (27%) and the risk was substantially lower with trastuzumab and paclitaxel (13%) or with trastuzumab alone (3-7%) (33). A pivotal trial of trastuzumab plus chemotherapy in MBC did not identify any unexpected adverse events with the use of long-term (up to 40+ months) trastuzumab (22). On the basis of available data on the use of trastuzumab in the adjuvant setting, cardiotoxicity seems to be treatable and mostly reversible and the risk of severe cardiac dysfunction ranges from 0.6 to 3.9% (32). Adjuvant trastuzumab trials have led to the introduction of rules for cardiac monitoring and the cessation of therapy (34,35). The incidence of cardiac dysfunction was 0-9.4% experiencing a decrease of >10% in LVEF when trastuzumab was added to neoadjuvant chemotherapy (36,37). In contrast to the early experience in MBC, concurrent neoadjuvant treatment with anthracycline-based regimen and trastuzumab appears to have an acceptable cardiac toxicity profile. Clinical evaluation prior to treatment with trastuzumab and anthracyclines in the neoadjuvant setting should include careful screening for cardiac risk factors (i.e., pre-existing cardiac diseases, baseline LVEF 50-55% in patients >65 years with hypertension, diabetes, or smoking habit and with BMI >25) and restriction of the cumulative anthracycline dose. Trastuzumab must be avoided if baseline LVEF is <50%.

Marked improvement has been observed in patients with HER2-positive breast cancer since the widespread use of trastuzumab; however, approximately 10% of patients develop a distant recurrence following adjuvant trastuzumab-based chemotherapy and all patients with MBC eventually develop disease progression (38). Furthermore, the risk of cardiotoxicity currently precludes certain patients from trastuzumab treatment, limiting the choice of agents that can be used concurrently with trastuzumab. Therefore, the development of novel targeted agents for use in HER2-positive breast cancer remains clinically significant.

Pertuzumab. Pertuzumab (Omnitarg; Genentech/Roche, South San Francisco, CA, USA) is an investigational fully humanized monoclonal antibody that targets the ECD of HER2 at a different site to trastuzumab and is able to inhibit ligand-induced homo- and hetero-dimerization of HER2 with other EGFR family members, including HER1, HER3 and HER4 (39,40). Early clinical data showing only modest activity as a single agent (41) and preclinical data showing enhanced antitumor activity for the combination of pertuzumab plus trastuzumab (42) have led investigators to focus on future clinical studies of pertuzumab in combination with trastuzumab. In a phase II trial evaluating the combination of pertuzumab and trastuzumab, a 24.2% RR and a 50% clinical benefit rate in 66 patients with HER2-positive MBC that progressed after trastuzumab-based therapy was reported (43). The promising results strongly demonstrate that pertuzumab can partially reverse trastuzumab resistance and the combination of the two antibodies can result in a synergistic efficacy. Combinations of pertuzumab and trastuzumab with chemotherapy have also being evaluated. A recently published clinical study that randomly assigned 808 patients with HER2-positive MBC to receive trastuzumab plus docetaxel with or without the combination of pertuzumab as first-line treatment demonstrated that the combination of pertuzumab plus trastuzumab plus docetaxel significantly prolonged PFS as compared with placebo plus trastuzumab plus docetaxel (18.5 vs. 12.4 months), and the interim analysis of OS showed a strong trend in favor of pertuzumab plus trastuzumab plus docetaxel (44). Pertuzumab has been approved by the US Food and Drug Administration in the first-line treatment of HER2-positive MBC (45). In a phase II randomized study of neoadjuvant setting, this dual-targeted drug combination plus docetaxel resulted in a statistically significant increase in pCR as compared with trastuzumab or pertuzumab plus docetaxel (45.8 vs. 29.0 or 24.0%), and a pCR rate of 16.8% in patients with targeted therapy only (no chemotherapy) (46). Recent findings suggest the addition of pertuzumab to trastuzumab in HER2-positive breast cancer is a therapeutic option in the neoadjuvant setting (47). At present, there are ongoing studies with pertuzumab in the adjuvant setting.

Since trastuzumab and pertuzumab are structurally similar and target HER2, additive toxicity is expected when the two drugs are administered concurrently. The tolerability of pertuzumab in combination with trastuzumab have being evaluated in several randomized trials in patients with HER2-positive breast cancer. In a phase II trial of 66 patients, cardiotoxicity was less of an issue with only three patients experiencing an asymptomatic LVEF decline of ≥10% and an absolute LVEF of <50%, and there were no withdrawals due to cardiac-related events (43). A recently published clinical study also demonstrated that the combination of pertuzumab plus trastuzumab plus docetaxel did not increase cardiac toxic effects (44). In general, the combination of pertuzumab and trastuzumab was well tolerated. However, the data on cardiac safety with pertuzumab should be interpreted with caution as the trials were conducted in carefully selected patients.

Trastuzumab-DM1. Trastuzumab-DM1 (T-DM1; Genentech/Roche, South San Francisco, CA, USA) is a novel chemistry-driven antibody-drug conjugate combining trastuzumab with a potent antimicrotubule agent, DM1 (a derivate of the cytotoxic chemotherapy agent maytansine). This molecule is targeted to HER2-positive cancer cells and releases DM1, thereby inhibiting the assembly of cellular microtubules (48). In trastuzumab-DM1, trastuzumab, not only retains the known mechanisms of action of trastuzumab, but also acts as a carrier that delivers DM1 to the tumor cells labelled with HER2, rendering DM1 less toxic and more effective (49). In a phase II

study of 110 patients with heavily pretreated HER2-positive MBC, trastuzumab-DM1 demonstrated that single-agent activity yielded a RR of 41.3% and PFS of 7.3 months in patients with HER2-positive MBC who had previously received the two HER2-directed therapies and multiple chemotherapeutic agents (50). A randomised phase II trial of trastuzumab-DM1 vs. trastuzumab/docetaxel in first-line, HER2-positive MBC demonstrated significant increases in RR (47.8 vs. 41.4%) and PFS (14.2 vs. 9.2 months) with trastuzumab-DM1 compared with the control arm, respectively (51,52). A phase Ib/II study evaluating the combination of trastuzumab-DM1 and pertuzumab in patients with previously untreated and relapsed HER2-positive MBC yielded a RR of 57.1% in previously untreated patients and a RR of 34.8% in relapsed patients (53). Data from the ongoing phase III trials of trastuzumab-DM1 and combination with various agents remain to be reported.

Toxicities of trastuzumab-DM1 were mild and reversible, and included thrombocytopenia, elevated transaminases, fatigue, nausea, and anemia (49). No dose-limiting cardiotoxicity was observed (50).

3. Tyrosine kinase inhibitors

Lapatinib. Lapatinib (Tykerb; GlaxoSmithKline, London, UK) is a dual, orally administered small molecule tyrosine kinase inhibitor of HER1 and HER2, which binds reversibly to the intracellular ATP-binding pocket of the two receptors and inhibits receptor autophosphorylation, preventing the activation of downstream cellular signals that promote tumor cell survival and proliferation (54,55). Lapatinib was approved in combination with capecitabine for the treatment of advanced or metastatic HER2-positive breast cancer based on the pivotal phase III trial in which 324 patients pretreated with an anthracycline, taxane and trastuzumab were randomized to receive capecitabine plus lapatinib or capecitabine alone (56). This trial showed that the addition of lapatinib to capecitabine significantly increased TTP (8.4 vs. 4.4 months) vs. capecitabine alone (56). The EGF30001 phase III trial which compared lapatinib plus paclitaxel with paclitaxel alone in the first-line setting demonstrated that treatment with paclitaxel plus lapatinib resulted in statistically significant improvements compared with paclitaxel alone in TTP (36.4 vs. 25.1 weeks), event-free survival (35.1 vs. 21.9 weeks) and RR (63.3 vs. 37.8%) (57). In addition to trials using lapatinib plus capecitabine or paclitaxel combination therapy, clinical trials of lapatinib and other chemotherapy agents, such as nab-paclitaxel, cisplatin and gemcitabine, have also exhibited positive results (58,59). In the EGF30008 phase III trial, which compared lapatinib plus letrozole with letrozole alone in treatment-naïve post-menopausal patients with hormone receptor-positive MBC, a 5.2 month improvement in PFS was evident in the lapatinib plus letrozole arm (8.2 vs. 3.0 months) (60). Dual HER2 blockade with lapatinib and trastuzumab was also assessed in a phase III trial of lapatinib plus trastuzumab comparing lapatinib alone in patients with HER2-positive MBC whose disease had progressed on trastuzumab. The trial demonstrated a significant 4.5 month median OS improvement with lapatinib plus trastuzumab compared with lapatinib alone and support dual HER2 blockade, thus offering a chemotherapy-free option for patients with heavily pretreated HER2-positive MBC (61). Lapatinib monotherapy yielded a RR of 24% as first-line treatment (62) and a RR of 5.1% in heavily pretreated patients (63).

The brain is a common metastatic site for HER2-positive breast cancer. Results of one study suggest that almost 50% of patients treated with trastuzumab develop brain metastases (64). However, poor results of systemic treatment of brain metastases in HER2-positive breast cancer have been obtained, likely due to the inability of systemic therapies, including trastuzumab, to cross the blood-brain barrier. Although lapatinib is a small molecular compound which may penetrate the blood-brain barrier easily and achieve an effective concentration level in the cerebrospinal fluid, it may also control brain metastasis. A potential role for lapatinib in reducing brain metastases became apparent in an exploratory analysis of data from a phase III trial of lapatinib plus capecitabine (56,65). The analysis demonstrated that lapatinib plus capecitabine treatment was associated with a lower rate of brain tumor progression, compared with capecitabine alone (65). This finding led to several trials of patients with brain metastases treated with lapatinib, with the results suggesting that lapatinib plays a role in the prevention and management of brain metastases in patients with HER2-positive breast cancer (66-68).

While the clinical evidence supported the use of lapatinib in the metastatic settings, lapatinib was evaluated in the neoadjuvant setting in several prospective randomized trials. A meta-analysis of randomized trials that compared the addition of lapatinib vs. trastuzumab or their combination to neoadjuvant chemotherapy in HER2-positive breast cancer showed that a significant increase of pCR rate was observed in the chemotherapy plus trastuzumab and lapatinib arm compared with chemotherapy plus trastuzumab [risk ratio of 1.39, 95% CI, 1.20-1.63; P<0.001], pCR rate was higher in the chemotherapy plus trastuzumab arm vs. chemotherapy plus lapatinib (risk ratio of 1.25, 95% CI, 1.08-1.43; P=0.003), and grade III-IV toxicities were statistically more frequent in patients receiving chemotherapy plus lapatinib (69). These data added further evidence supporting the superiority of a dual-HER2 inhibition for the treatment of HER2-positive breast cancer. The direct comparison of trastuzumab and lapatinib showed that lapatinib is inferior in terms of pCR and associated with a higher risk for toxicity in the neoadjuvant setting. Thus, use of lapatinib in the neoadjuvant setting should be considered experimental. In addition to trials in the neoadjuvant setting, several adjuvant studies of lapatinib are ongoing. In the future, these trials should establish whether lapatinib and trastuzumab are to be used together or sequentially, and which settings are optimal for the two agents.

The systemic analysis of lapatinib demonstrated that it is well tolerated with manageable toxic effects (70). Although the same pathway was targeted, no increase in symptomatic cardiac events with the addition of lapatinib occurred, and the incidence of cardiac toxicity was lower with lapatinib compared with trastuzumab. Grade 3/4 treatment-related toxicities of lapatinib are uncommon with grade 3 diarrhea reported in 7% and all other toxicities (not specified) in <3% of patients.

Neratinib. Neratinib (HKI-272; Pfizer, New York, NY, USA) is an irreversible, orally administered small molecule TKI of

HER1, HER2 and HER4 that covalently binds to the cysteine residues of the ATP-binding portion of the HER TKs (71). An open-label, phase II multicenter trial of single-agent neratinib in 136 patients with HER2-positive MBC showed a RR of 24% in patients previously treated with trastuzumab, and a RR of 56% in trastuzumab-naïve patients. PFS at 16 weeks was 59 and 78%, respectively (72). No grade 3 or 4 cardiotoxicity related to neratinib was reported, but grade 3 and 4 diarrhea was the most frequently occurring adverse effect. In combination with vinorelbine in patients pretreated with trastuzumab, RRs of 41 and 8% were observed in those who had not and had received prior lapatinib, respectively (73). The potential combinations of neratinib with various chemotherapy agents, trastuzumab, lapatinib and new targeted agents in the metastatic, adjuvant and even neoadjuvant settings are under investigation. These results and future perspectives remain to be elucidated and reported.

Afatinib. Afatinib (BIBW 2992; Boehringer Ingelheim, Ingelheim, Germany) is a novel, oral, small-molecule TKI that covalently binds and irreversibly blocks all kinase-competent HER family members (74). In an open-label, single-arm phase II study which explored afatinib activity in 41 HER2-positive breast cancer patients progressing after trastuzumab treatment, 4 patients had partial responses and 15 patients had stable disease. Median PFS was 15.1 weeks, and median OS was 61.0 weeks. The most frequently occurring grade 3 treatment-related adverse events were diarrhea (24.4%) and rash (9.8%). Afatinib monotherapy had promising clinical activity in heavily pretreated HER2-positive breast cancer patients following progression on trastuzumab (75). An ongoing global phase III study is evaluating afatinib plus vinorelbine versus trastuzumab plus vinorelbine in patients with HER2-positive MBC progressing after trastuzumab treatment. Afatinib is also under investigation in various combinations and in the neoadjuvant setting.

4. Conclusion

Treatment specifically targeted at HER2 has improved survival during the past decade in patients with HER2-positive breast cancer. Nevertheless, resistance remains a challenge, particularly in the metastatic setting. With the deepening fundamental understanding of molecular correlations and characterization of breast cancer, new agents are in clinical development, including those directed at the HER2 receptor itself and those targeting downstream effectors and interacting compensatory signaling pathways such as hsp90, mTOR and IGF-1R inhibitors. Such results are likely to useful in the prognotic effect of HER2-positive breast cancer.

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