Current Standards and New Treatment Insights in HER2-Driven Metastatic Breast Disease

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Abstract

Overexpressing or amplified human epidermal growth factor receptor 2 (HER2) is found in 20% to 25% of breast cancers, which is associated with aggressive biology and worse overall survival. HER2-targeted therapies have dramatically improved the clinical outcomes of patients with HER2-positive breast cancer, both in neoadjuvant/adjuvant and in metastatic settings. For metastatic breast cancer (MBC), HER2 targeted drugs approved by the Food and Drug Administration include trastuzumab, lapatinib, pertuzumab, and trastuzumab emtansine (T-DM1). This article reviews the optimal management of HER2-targeted therapies and describes emerging novel therapies in the treatment of HER2-positive MBC.

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Introduction

Despite significant advances in the past decade, breast cancer remains the second leading cause of death and the most common cancer in women in the United States.[1] HER2 is a cell-surface receptor that signals cell growth and survival through the activation of downstream signaling pathways. The HER2 oncogene is amplified and/or overexpressed in 20% to 25% of breast cancers[2] and is associated with an aggressive phenotype, including high-grade tumors, faster growth rates, and worse survival.[2,3] Approved HER2-targeted therapies include trastuzumab, lapatinib, pertuzumab, and T-DM1, all of which have dramatically changed the treatment landscape and improved the survival of patients with this aggressive type of cancer.[4-15] However, in most patients with HER2-positive metastatic breast cancer (MBC), resistance develops eventually, for which novel targeted therapies are urgently needed.[16-18] This article presents the optimal management of anti-HER2 therapies in MBC. In addition, new therapeutic strategies and drugs that are currently in clinical trials are also reviewed.

Optimal Treatment for Patients With HER2-Positive MBC

First-Line Treatment

The CLEOPATRA trial was a randomized phase III study in which 808 patients with HER2-positive MBC were randomized 1:1 to either docetaxel, trastuzumab, and placebo (DH) or to docetaxel, trastuzumab, and pertuzumab (DHP) in the first-line setting.[9,19] With a median follow-up of 50 months, patients who received DHP demonstrated a superior median progression-free survival (PFS; 18.7 vs 12.4 months; hazard ratio (HR), 0.68; 95% confidence interval [CI], 0.58-0.80; *P* <.001) and overall survival (OS; 56.5 vs 40.8 months; HR, 0.68; 95% CI, 0.56-0.84; *P* <.0001). This pivotal study altered the paradigm in the first-line treatment of patients with HER2-positive MBC, for which trastuzumab with a taxane plus pertuzumab is the preferred first-line approach. Notably, a phase II clinical trial evaluating HP with paclitaxel (T) revealed a median PFS of 19.5 months, with a favorable toxicity profile, and thus was endorsed by the National Comprehensive Cancer Network (NCCN) as another first-line option.[20]

Second-Line Treatment

Continuing HER2-targeted therapy in the second-line setting beyond progression is appropriate. In the randomized, phase III EMILIA trial, T-DM1 was superior to capecitabine plus lapatinib in PFS (9.6 vs 6.4 months; HR, 0.65; 95% CI, 0.55-0.77; *P* <.001) and OS (30.9 vs 25.1 months; HR, 0.68; 95% CI, 0.55-0.85; *P* <.001) in patients who had prior taxane and trastuzumab therapy.[13] Based on this trial, T-DM1 is considered the preferred second-line therapy. Of note, the MARIANNE study demonstrated that T-DM1 and T-DM1 plus pertuzumab were noninferior, but not superior, to standard taxane and trastuzumab in the first-line setting.[21] In addition, the MARIANNE study failed to show that the addition of pertuzumab to TDM-1 was better than TDM1 alone (HR 0.91; 95% CI, 0.73–1.13). Thus, T-DM1 is not a preferred first-line treatment, but remains an optimal second-line option.

Third-Line Treatment and Beyond

Multiple treatment options are available when disease progresses after second-line therapies. If the patient has not received T-DM1, this therapy is recommended because of the PFS and OS benefits shown in the TH3RESA trial.[14,22] Other options include trastuzumab plus lapatinib,[23,24] trastuzumab plus capecitabine, lapatinib plus capecitabine, and trastuzumab plus other agents. Of note, in

patients with hormone receptor (HR)–positive disease, endocrine therapy plus HER2 blockade (trastuzumab or lapatinib) is also an option.[25,26] If the patient has not received pertuzumab, clinicians may offer pertuzumab per NCCN guidelines.[27]

What about the activity of pertuzumab-based therapy after prior pertuzumab treatment? One such phase II study is ongoing.[28] Another phase II study is randomizing patients previously treated with T-DM1 (prior pertuzumab allowed) to trastuzumab or pertuzumab/trastuzumab (both arms with chemotherapy), and prior pertuzumab is allowed (NCT02229149). These results are highly anticipated.

Novel Treatments for Patients With HER2-Positive MBC

Biosimilar Compared With Trastuzumab

Given the price of trastuzumab, globally accessible alternatives are critically needed. A biosimilar is structurally and functionally similar to the reference product with little difference in safety, purity, and potency, and, ideally, no difference in efficacy. HERITAGE is a double-blind, randomized clinical trial comparing efficacy and safety of MYL-1401O versus trastuzumab (both combined with a taxane) in patients with HER2-positive MBC in the first-line setting.[29] Patients were randomized to receive either MYL-1401O or trastuzumab (both with docetaxel or paclitaxel) for a minimum of 8 cycles, and both biologics were continued until progression. Overall, MYL-1401O was found to be equivalent to trastuzumab. The primary endpoint was overall response rate (ORR) at 24 weeks, and it was 69.6% for MYL-14010 compared with 64% for trastuzumab, with a ratio of ORR for MYL 1401O/trastuzumab of 1.09; both 90% CI (0.97-1.21) and 95% CI (0.95-1.24) were within the predefined equivalence margin. Safety was comparable with both biologics. Thus, MYL-1401O may become a new treatment option for patients with HER2-positive MBC who may not have access to trastuzumab, and this is just one of several biosimilars in development.

Novel HER2 Tyrosine Kinase Inhibitor

Approximately 37% of patients with HER2-positive MBC experience brain metastasis, which includes 7% at diagnosis and 30% over the course of their disease.[30] Brain metastasis is associated with worse outcome, and optimal treatment remains one of the biggest challenges. ONT-380 is a potent, highly selective, small-molecule tyrosine kinase inhibitor (TKI) of HER2. In a phase Ib study combining ONT-380 and T-DM1 in patients previously treated with a taxane and trastuzumab, the combination demonstrated encouraging efficacy with ORR of 47% and median PFS of 8.2 months.[31] Notably, in those with brain metastasis, the ORR in central nervous system (CNS) disease was 36% overall. In terms of adverse events, the combination therapy was reasonably well tolerated, with grade 3 diarrhea occurring in only 4% of patients.[31]

The efficacy of ONT-380 in CNS appears favorable when reviewing the activity of other agents in terms of CNS ORR from lapatinib (2.6%-6%), capecitabine and lapatinib (6%), and neratinib (8%).[32-34] Another small molecule is tesevatinib (KD019), a TKI against EGFR, HER2, VEGFR 2/3, and the Src family of kinases, which also demonstrated early efficacy signal systemically and in CNS in a phase I trial in patients with heavily pretreated HER2-positive MBC. In the 10 patients treated at dosages of at least 300 mg orally daily, 4 patients had brain metastases; 3 out of 4 experienced no progression in their CNS disease while on tesevatinib therapy.[35] Overall, 4 out of 10 subjects had stable disease (SD) after 2 cycles (6 weeks), and 3 had SD after 4 cycles (12 weeks) of therapy.[35] We look forward to further development of these 2 drugs.

Another HER2 TKI is neratinib, a potent, low-molecular-weight, irreversible pan-TKI with activity against HER1, HER2, and HER4. Single-agent neratinib has shown promising clinical activity in patients with previous trastuzumab exposure, with ORR of 24% and median PFS of 22.3 weeks, and in trastuzumab-naïve patients the ORR was 56% and median PFS was 39.6 weeks.[36] Neratinib in combination with capecitabine showed promising activity in resistant HER2 MBC in a phase I/II clinical study, with ORR of 64% (n = 39/61) and median PFS of 40 weeks, and ORR 57% (n = 4/7) and median PFS of 36 weeks, in patients without and with prior lapatinib, respectively.[37] An ongoing randomized phase III study (NALA) is comparing neratinib plus capecitabine versus lapatinib plus capecitabine (NCT01808573). Depending on the results of this trial, neratinib may become another potential option in the treatment of HER2-positive MBC beyond the second line.

Other Novel Therapies

MM-302 is an antibody-drug conjugated liposomal doxorubicin. A phase I trial of MM-302 has shown it to be active in a heavily pretreated population, with ORR of 11.3% and median PFS of 7.6 months.[38] It is being investigated in combination with trastuzumab versus physician's choice of chemotherapy plus trastuzumab in a randomized phase II trial (HERMIONE) in patients with anthracycline-naïve, locally advanced or HER2-positive MBC who had received prior treatment with pertuzumab and T-DM1.[39] Anti-HER3 antibodies, such as LJM 716, are currently being evaluated with BYL719 (PI3K inhibitor) and trastuzumab in HER2-positive MBC, and we look forward to mature data.[40]

Activation of signaling pathways involving the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway has been suggested to contribute to resistance to HER2-targeted therapies. Several mTOR, PI3K, and dual PI3K/mTOR inhibitors have been shown to restore sensitivity to HER2-targeted therapy in in vitro and in vivo models.[41-45] The phase III trial BOLERO-1 randomized patients to everolimus, an mTOR inhibitor, or placebo, both with trastuzumab and weekly

paclitaxel in the first-line setting.[46] Overall, this was a negative trial and demonstrated no PFS benefit with the addition of this mTOR inhibitor (14.95 vs 14.49 months; HR, 0.89; 95% CI, 0.73-1.08; *P* =.1166). BOLERO-3 was a phase III trial that evaluated the combination of everolimus, or placebo, both with trastuzumab and vinorelbine in trastuzumab-refractory, advanced disease.[47,48] This study demonstrated a PFS gain from 5.78 to 7.0 months (HR, 0.78; 95% CI, 0.65-0.95; *P* =.0067) with the addition of everolimus. However, toxicities were significantly higher with the addition of everolimus (with a modest gain in PFS), and thus this regimen is not adopted as a standard second-line option.

An exploratory biomarker study of both BOLERO-1 and 3 trials suggests that patients with PI3K mutations, hyperactive PI3K pathway, or PTEN loss may derive the most benefit from everolimus, but further work is needed to validate these findings.[49] Other mTOR inhibitors undergoing phase I/II clinical trials for patients with resistance to HER2-targeted therapies include temsirolimus and INK128. Additionally, several inhibitors of the PI3K and Akt pathways are currently being evaluated in clinical trials in this disease setting,[50] further supporting the enthusiasm in the field of targeting the PI3K/Akt/ mTOR pathway in overcoming resistance to HER2-targeted therapies.

Hsp90 regulates the folding, stability, and function of many cellular proteins that are relevant to breast cancer pathogenesis. HER2 is one of the most sensitive Hsp90 clients. Multiple Hsp90 inhibitors have been evaluated for HER2-positive breast cancer and showed clinical benefit in patients with HER2-positive breast cancer.[51-56] Ganetespib is a small-molecule, nongeldanamycin Hsp90 inhibitor, and in a phase II trial showed activity in trastuzumab-refractory HER2-positive MBC with an ORR of 15%.[55] In a phase I trial, ganetespib in combination with paclitaxel and trastuzumab in trastuzumab-resistant, HER2-positive MBC was shown to be safe and well tolerated, with a promising ORR of 25%, warranting further study.[56]

Dysregulation of the cell cycle is one of the defined hallmarks of cancer, and cyclin-dependent kinase (CDK) 4/6 complex is dysregulated in breast cancer. CDK4/6 inhibitors, in combination with an aromatase inhibitor (AI), improves PFS over treatment with an AI alone in patients with newly diagnosed HR-positive, HER2-negative MBC.[57-59] A few ongoing trials are evaluating the efficacy of palbociclib, abemaciclib, and ribociclib combined with a standard anti-HER2–based therapy (ie, trastuzumab, T-DM1), and we eagerly await the results of these trials (NCT02448420, NCT02675231, NCT02657343).

Currently, work is ongoing to test the efficacy of other novel inhibitors, such as those against the histone deacetylase and androgen receptor pathways, in patients with HER2-positive breast cancer,[60] and we look forward to seeing emerging data from these trials (NCT00567879, NCT02091960).

Conclusions

Significant progress has been made in the treatment of patients with HER2-positive MBC. Based on current evidence from clinical trials, a taxane plus HP is the optimal first-line therapy, with T-DM1 to follow in the second line after disease progression. In addition, multiple options are available for third line and beyond. When appropriate, patients should be offered clinical trials with novel therapies or strategies. Fortunately, many patients are living significantly longer because of available HER2-targeted agents. However, many will experience brain metastases. There appear to be several novel agents that confer both CNS and systemic disease control, and we eagerly await the completion of these trials. Furthermore, we should be reminded that trastuzumab, the first approved anti-HER2 antibody, is not always available to all patients. With the emergence of biosimilars, more patients may be able to be treated with equally effective therapies. Finally, progression of disease despite a period of disease control occurs far too frequently, and thus in addition to evaluating novel therapies, exploring biomarkers as predictors of response or resistance remains critically important.

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