Published in final edited form as:

Clin Breast Cancer. 2009 June ; 9(Suppl 2): S50–S57. doi:10.3816/CBC.2009.s.005.

Treatment of HER2-Positive Metastatic Breast Cancer Following Initial Progression

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Abstract

Significant advances in molecular-targeted therapies have provided more effective and less aggressive forms of therapy for patients with HER2-overexpressing metastatic breast cancers. Despite the initial encouraging results of many therapeutic randomized trials that have been undertaken in this setting, *de novo* and acquired resistance to trastuzumab, the first anti-HER2 monoclonal antibody to demonstrate significant activity in this setting, can occur. Because recent studies strongly support a role for trastuzumab in not only the management of metastatic disease but also the adjuvant setting for HER2-overexpressing breast cancers, the clinical problem of trastuzumab resistance is becoming increasingly important. Specific recommendations for the optimal treatment of HER2-overexpressing metastatic disease are challenging because considerable advances in the field have been made. This article will review some of the main points to be considered for decision-making in anti-HER2 treatment in the metastatic setting: (1) the benefit of continued trastuzumab after progression on a first-line trastuzumab-containing regimen, (2) novel agents that have been recently added to the plethora of drugs available to treat HER2-overexpressing breast cancers, and (3) molecular mechanisms that contribute to trastuzumab resistance. These issues are imperative in identifying novel therapeutic targets with the goal of increasing the magnitude and duration of response to trastuzumab-based treatment.

Keywords

Anthracycline; Antiangiogenesis; Lapatinib; Neratinib; Paclitaxel; Pertuzumab; Trastuzumab

Introduction

Patients with metastatic breast cancer (MBC) are unlikely to be cured of their disease by any means. A complete remission (CR) from systemic therapy, which is a prerequisite for cure, is uncommon, and only a fraction of the patients who have a CR remain progression free for a prolonged period.^{1,2} Over the past years, advances in molecular-targeted therapies have provided more effective and less aggressive forms of therapy in this setting. Lately, the development of new strategies for the treatment of breast cancer has focused on not only target identification but also understanding the expression, regulation, and function of

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Dr. Mayer has no relevant relationships to disclose.

This article includes the discussion of investigational and/or unlabeled use of drugs, including the use of trastuzumab beyond progression on previous trastuzumab therapy; trastuzumab in combination with lapatinib, pertuzumab, vinorelbine, docetaxel, cisplatin, gemcitabine, capecitabine, tanespimycin, alvespimycin, bevacizumab, carboplatin, or anastrozole; lapatinib monotherapy or in combination with paclitaxel, trastuzumab, letrozole, or fulvestrant; and trastuzumab-DM1, canertinib (CI-1033), CL-387,785, and neratinib for the treatment of patients with HER2-positive metastatic breast cancer.

critical signaling pathways involved in breast cancer initiation and progression. Therapies for breast cancer should be guided by biologic features of the tumor, such as hormone sensitivity or HER2 overexpression. Notable examples include the successful use of hormonal therapy (eg, aromatase inhibitors [AIs] or tamoxifen) for women with hormone-sensitive (estrogen receptor [ER]– and/or progesterone receptor [PgR]–expressing) tumors³ and the use of anti-HER2 therapies for women with overexpression of the aforementioned protein.⁴

HER2/*neu* (HER2) is a 185-kDa oncoprotein (p185) that is overexpressed in about 30% of invasive breast cancers.^{5,6} HER2 overexpression is associated with not only resistance to cytotoxic and endocrine therapy but also an aggressive biologic behavior that translates into a shorter disease-free interval and overall survival (OS) in patients with early and advanced breast cancer.⁷ Trastuzumab, a humanized monoclonal antibody (MoAb) against HER2/*neu* (murine MoAb 4D5 combined with human immunoglobulin [Ig]G) that binds the ectodomain of the HER2 receptor, has been approved by the US Food and Drug Administration (FDA) for the treatment of HER2-overexpressing breast cancer in both the adjuvant and metastatic settings. Despite initial encouraging results, the response rate (RR) with trastuzumab is ~40% as a single agent in the first-line treatment of MBC, and the median duration of response is between 9 and 12 months.^{8–10} This suggests that both de novo and acquired resistance to trastuzumab occur.

Because recent studies strongly support a role for trastuzumab in not only the management of metastatic disease but also in the adjuvant setting for HER2-overexpressing breast cancers,^{11–13} the clinical problem of trastuzumab resistance is becoming increasingly important. Despite the many therapeutic randomized trials that have been undertaken in patients with HER2-overexpressing breast cancer, the fact that the field is evolving so rapidly makes it difficult to make specific recommendations for the optimal treatment of HER2-overexpressing metastatic disease. This article will review some of the main points to be considered for decision-making in anti-HER2 treatment in the metastatic setting, such as the benefit of continued trastuzumab after progression on a first-line trastuzumab-containing regimen, which has not been adequately validated in a prospective fashion; novel agents that have been recently added to the plethora of drugs available to treat HER2-overexpressing breast cancers; and molecular mechanisms that contribute to trastuzumab resistance. These issues are imperative in identifying novel therapeutic targets with the goal of increasing the magnitude and duration of response to trastuzumab-based treatment.

Trastuzumab

Monoclonal antibodies, such as trastuzumab, that target the HER2 ectodomain sensitize HER2-overexpressing cells to apoptotic stimuli by interfering with HER2 activation and HER2-dependent gene expression, resulting in cell-cycle progression and cellular differentiation. Now a fundamental part of the therapy for patients with HER2-overexpressing MBCs, trastuzumab has several mechanisms of action, including G₁ arrest via upregulation of the cyclin-dependent kinase (CDK) inhibitor p27^{14–18}; induction of antibody-dependent cellular cytotoxicity through interaction with CD16-positive immune effector cells^{14–16}; receptor downregulation from the tumor cell surface^{15,16}; stimulation of HER2 homodimerization and hence prevention of heterodimer formation¹⁵; inhibition of postreceptor downstream signal transduction^{14,16,19}; inhibition of the production of angiogenic factors, such as vascular endothelial growth factor (VEGF)^{15,19}; and inhibition of constitutive HER2 cleavage/shedding mediated by metalloproteases, which results in the release of soluble extracellular domain and constitutive activation of the remaining membrane-associated HER2 domain (the truncated receptor known as p95).^{15,16,20–22}

A landmark randomized phase III trial comparing first-line standard chemotherapy (doxorubicin/cyclophosphamide or paclitaxel) with or without trastuzumab in 469 women with HER2-overexpressing MBC showed that the trastuzumab-based combination therapy not only reduced the relative risk of death by 20% at a median follow-up of 30 months but also significantly increased the time to disease progression, RRs, durations of response, and time to treatment failure (TTF).⁴ Nevertheless, the concurrent use of trastuzumab with the anthracycline regimen was reported to significantly increase the risk of cardiac dysfunction to unacceptable levels. The increase in OS seen with first-line trastuzumab plus chemotherapy for women with HER2-overexpressing MBC has made its use the standard of care in this setting. For women who cannot or are unwilling to receive cytotoxic chemotherapy for MBC, the use of single-agent trastuzumab as first-line treatment is a valid option. In women with HER2-overexpressing 3+ tumors verified by immunohistochemistry (IHC) or those with HER2/*neu* gene amplification as detected by fluorescence in situ hybridization, the RR is about 35%. About 50% of responders are free of progression after 1 year. The median survival in patients with HER2-overexpressing tumors is about 24 months, suggesting that patients do not incur a major survival disadvantage if they receive trastuzumab alone as first-line therapy for metastatic disease.⁹

Subsequent trials evaluated the role of trastuzumab with other chemotherapy agents, such as vinorelbine. This combination turned out to be very safe and well tolerated, and in the first-line treatment of women with MBC that overexpressed HER2/*neu*, objective RRs (ORRs) were in the order of 68%, with a median TTF of 5.6 months.²³ An impressive finding is the fact that almost 40% of the patients enrolled in this phase II trial were free of progression after 1 year. The efficacy of trastuzumab in combination with other agents, such as docetaxel,^{24,25} cisplatin,²⁶ and gemcitabine,²⁷ has also been assessed. Of note, none of the aforementioned trials included patients who received trastuzumab in the adjuvant setting.

Other HER2 Inhibitors

Lapatinib

Lapatinib is a dual adenosine triphosphate-competitive, small-molecule tyrosine kinase inhibitor (TKI) against both epidermal growth factor receptor (EGFR) and HER2.²⁸ Lapatinib potently inhibits the catalytic activity of p95^{HER2},²⁹ which is relevant in HER2-overexpressing tumors in which the oncogene product is expressed as a kinase-active, 95-kDa cytosolic fragment that lacks the trastuzumab-binding epitope and, therefore, can potentially allow the cancer cell to escape the action of trastuzumab.

Lapatinib has demonstrated antitumor activity both in vitro and in vivo against HER2-overexpressing breast cancer cells.^{30,31} In breast cancer cells that develop resistance to trastuzumab as a result of overexpression of ErbB ligands and EGFR, lapatinib inhibits HER2 activity and the growth of the resistant cells.³² It is also active as a single agent in patients with HER2-overexpressing cancers either as first-line therapy or after escape from trastuzumab.^{33,34} In the study that led to its registration by the FDA, women with HER2-overexpressing locally advanced or metastatic breast cancer that had progressed after treatment with regimens containing anthracyclines, taxanes, and trastuzumab were randomized to receive capecitabine with or without lapatinib.³⁴ Median progression-free survival (PFS) and median time to progression (TTP) were almost doubled by the addition of lapatinib in the cases in which HER2 overexpression was centrally confirmed, without an increase in severe toxicity or symptomatic cardiac events. Another randomized trial of paclitaxel with or without lapatinib in patients treated with first-line therapy for MBC reported similar outcomes in the 91 patients with HER2-overexpressing cancers; the addition of lapatinib improved median TTP to 8.1 months compared with 5.8 months in the paclitaxel-alone arm.³⁵ Data supporting the strategy of complete inhibition of the HER2

pathway comes from a randomized trial of lapatinib plus trastuzumab compared to lapatinib alone in patients with heavily pretreated HER2-overexpressing MBC that had progressed on trastuzumab.³⁶ Treatment with the combination improved median PFS from 8.1 to 12 months, doubled the clinical benefit rate (CBR) to 25%, and marginally improved OS. Interestingly, there was a 12.4% CBR in the single-agent lapatinib arm, which further confirms its activity after escape from trastuzumab. Unlike trastuzumab, lapatinib and other small-molecule HER2 kinase inhibitors have the potential to cross the blood-brain barrier. In the phase III pivotal lapatinib registration trial, despite being infrequent, central nervous system (CNS) metastasis occurred in fewer women in the combination arm than in the capecitabine arm.³⁴ This trend was confirmed in a phase II trial of lapatinib in 39 patients with HER2-overexpressing breast cancer and brain metastases,³⁷ in which a small but unmistakable number of responses were seen (1 patient had a partial response [PR] in the brain, and 7 patients [18%] were progression free at 16 weeks). Because patients with HER2-overexpressing MBCs live longer and are more prone to develop CNS metastasis, the potential CNS antitumor activity of small-molecule TKIs is an important subject of several prospective trials.

Pertuzumab

Pertuzumab is a humanized IgG1 MoAb that specifically binds an epitope in the dimerization domain of HER2 and, therefore, can block transactivation of HER2 by its ErbB coreceptors in cells with low and high HER2 levels,^{38,39} which in turn would prevent HER2 activation via heterodimerization with ligand-activated HER3. Clinically, the addition of pertuzumab to trastuzumab in patients with HER2-overexpressing breast cancers who had progressed on trastuzumab therapy resulted in a 40% CBR.⁴⁰

Trastuzumab-DM1

Antibody-drug conjugates (ADCs), MoAbs to which highly potent cytotoxic agents have been conjugated, represent a novel approach to conferring tumor selectivity on systemically administered antitumor therapeutics. Utilizing surface antigens that are tumor specific and/or overexpressed, ADCs are designed to focus the delivery of highly potent cytotoxic agents to tumor cells. The potential of this approach is to create a more favorable therapeutic window for such agents than could be achieved by their administration as free drugs.

Trastuzumab-DM1 (T-DM1) is a novel HER2 ADC. T-DM1 binds to HER2 with affinity similar to that of trastuzumab, promoting its antitumor activity by combining the action of trastuzumab with targeted delivery (receptor-mediated internalization followed by intracellular release) of the highly potent antimicrotubule maytansine derivative DM1⁴¹ to HER2-overexpressing cells. Clinical antitumor activity was observed in a phase I study of T-DM1 in which 6 of 24 patients previously treated with trastuzumab exhibited a PR.⁴² Treatment was well tolerated; reversible grade 4 thrombocytopenia was the main dose-limiting toxicity. The interim analysis of a phase II study of single-agent T-DM1 in 112 heavily pretreated patients (median number of chemotherapy regimens in the metastatic setting: 3; 50% of patients received previous lapatinib) was recently reported.⁴³ Of the 107 evaluable patients, the investigator-determined RR was 39% (independent review facility–reported RR of 29%), with similar rates observed in the 62 patients who had received prior trastuzumab and lapatinib. These data support T-DM1 as a valid option for patients who have progressed on previous anti-HER2 therapies.

Other Anti-HER2 Tyrosine Kinase Inhibitors

CI-1033, CL-387,785, and neratinib (HKI-272) are irreversible dual inhibitors of the EGFR and HER2 TKs. Of these, neratinib is in clinical development. In a phase I trial of this TKI, diarrhea, nausea, and asthenia were the main side effects.⁴⁴ Partial responses were observed

in heavily pretreated patients with trastuzumab-resistant HER2-overexpressing breast cancer, suggesting that these advanced tumors remained dependent on the HER2 oncogene. A recent phase II study in 136 patients (66 previously treated with trastuzumab and 70 trastuzumab-naïve) demonstrated a median PFS of 23 weeks in the evaluable trastuzumab-exposed patients and a median PFS of 40 weeks in the evaluable trastuzumab-naïve patients, confirming its antitumor activity in HER2-overexpressing breast cancers.⁴⁵

Trastuzumab Continuation After Progression

Several preclinical studies supported the need for chronic administration of trastuzumab, but optimal duration of therapy is unclear. There is a paucity of data addressing this issue, and in clinical practice, oncologists continue to use trastuzumab even after disease progression. This practice pattern was confirmed by a central registry program initiated in 2003 that collects information longitudinally from a large number of patients with HER2-overexpressing breast cancer during the course of their disease. RegisHER is a prospective longitudinal cohort study in MBC designed to understand treatment practice and outcomes.⁴⁶ Eligibility criteria include HER2-overexpressing MBC diagnosed within 6 months; such patients receive treatments according to the standard of care. Over 1000 patients have been enrolled, and about 75% of the patients who received chemotherapy plus trastuzumab continued trastuzumab with a different chemotherapy agent at progression.

In the absence of results from a randomized clinical trial, several retrospective studies attempted to clarify the optimal duration of trastuzumab therapy in the metastatic setting. An extension study of the pivotal phase III trial that led to the approval of trastuzumab as first-line therapy for HER2-overexpressing MBC evaluated the safety of continuing trastuzumab as monotherapy beyond disease progression.⁴⁷ Although not designed to evaluate efficacy, RRs and median response duration to second-line trastuzumab were similar for the patients who initially received chemotherapy alone and for those who initially received chemotherapy plus trastuzumab. In another retrospective analysis, trastuzumab alone or in combination with a different chemotherapy agent was continued beyond disease progression in 80 patients with HER2-overexpressing MBC⁴⁸ and yielded 32 responses. A third retrospective study analyzed 105 patients with HER2-overexpressing MBC who received 2 or more trastuzumab-containing regimens.⁴⁹ Objective RRs were similar for second-line compared with first-line therapy, and some patients who had not responded to first-line therapy responded to second-line therapy.

A multicenter study started in 2002 at The University of Texas M. D. Anderson Cancer Center randomized patients to receive vinorelbine with or without continuation of trastuzumab after progression on a previous trastuzumab-containing regimen to determine if continued treatment with trastuzumab beyond progression conferred clinical benefit to patients with HER2-overexpressing MBC. Only 16 patients were enrolled over 1 year, and the study was closed because of slow accrual. A similar nationwide Intergroup trial led by the Southwest Oncology Group, S0347, also failed to accrue in a timely manner and was closed.

One major barrier for patient enrollment in prospective clinical trials evaluating the continuation of trastuzumab is reluctance among physicians and patients to accept randomization to discontinue trastuzumab therapy after evidence of disease progression. Benefit from continued HER2 blockade after failure of trastuzumab has only recently been reported. The Treatment Beyond Progression (TBP) phase III study (GBG 26/Breast International Group [BIG] 3-05) randomly assigned 156 women with locally advanced or metastatic breast cancer progressing during trastuzumab treatment to capecitabine with or without trastuzumab.⁵⁰ There was a significantly higher ORR (49% vs. 25%) and median

PFS (8.5 months vs. 5.6 months) with combination therapy compared with capecitabine alone. Another phase III trial that assigned 296 women with trastuzumab-refractory MBC to lapatinib with or without trastuzumab revealed that the ORRs were similar between the treatment arms but that median PFS was significantly longer with combination therapy (12 months vs. 8.4 months), with a trend toward longer median survival (52 weeks vs. 39 weeks), compared with lapatinib alone.³⁶

In summary, trastuzumab's targeted activity, with direct antiproliferative effects, synergistic interaction with chemotherapy and targeted agents (such as lapatinib), and antiangiogenic effects, might support the feasible and overall safe approach of treatment beyond disease progression.

Molecular Mechanisms That Contribute to Trastuzumab Resistance

Insulin-like Growth Factor-1 Receptor Signaling

Higher levels of circulating insulin-like growth factor-1 (IGF-1) are associated with increased risk of several cancers, including breast cancer. In addition, preclinical data provide evidence that the IGF signaling pathway is aberrantly activated in breast cancer cells.^{51–54} IGF-1 signaling is known to activate several pathways involved in mitogenesis and cell survival.^{55,56} Lu et al demonstrated that the trastuzumab-induced growth inhibition in HER2-overexpressing cells can be compensated for by increased IGF-1 receptor (IGF-1R) signaling, resulting in resistance to trastuzumab.^{57,58} IGF-1R-mediated resistance to trastuzumab treatment appears to involve the phosphatidylinositol 3-kinase (PI3K) pathway, leading to enhanced degradation of p27. Recently, Nahta et al reported enhanced antitumor effects with lapatinib in combination with IGF-1R-specific antibodies in breast cancer cells.⁵⁹ In light of the cross-talk between IGF-1R and HER receptors, combining therapies targeting both pathways makes sense scientifically. Future clinical studies combining trastuzumab or lapatinib with IGF signaling inhibitors will address the contribution of the latter pathway to resistance to anti-HER2 therapies.

The PI3K/Akt Pathway

Both genetic and biochemical data suggest that activation of the PI3K/Akt survival pathway contributes to breast cancer development and tumorigenesis. In spontaneous breast cancers, *PTEN* mutations are found in approximately 5% of samples, and loss of heterozygosity of the *PTEN* locus is present in approximately 40%.^{60–62} Akt is a downstream target of many receptor-stimulated pathways involved in breast cancer, including ER- α , IGF-1R, EGFR, and HER2.^{63,64} Amplification of the *AKT2* gene is found in 3% of spontaneous breast cancers,⁶⁵ and an inverse relationship between ER status and Akt3 activity has been described in both breast cancer cell lines and tumor specimens.⁶⁶ Preclinical data suggest that disabling the PI3K/Akt pathway is a key component of the antitumor effects of trastuzumab⁶⁷ and that constitutively activated/forced expression of Akt could be associated with resistance to trastuzumab in HER2-overexpressing breast cancer cells.⁶⁸ Trastuzumab-resistant cells demonstrate elevated levels of phosphorylated Akt and Akt kinase activity compared with parental cells.⁶⁹ These resistant cells also show increased sensitivity to PI3K inhibitors. Nagata et al demonstrated that decreased levels of the *PTEN* phosphatase resulted in increased PI3K/Akt phosphorylation and signaling and blocked trastuzumab-mediated growth arrest of HER2-overexpressing breast cancer cells.⁷⁰ In *PTEN*-deficient cells, PI3K inhibitors rescued trastuzumab resistance in vitro and in vivo.

Recently, 2 sequential clinical trials that analyzed the effect of neoadjuvant trastuzumab and subsequently lapatinib as single agents for 3 and 6 weeks, respectively, in patients with locally advanced breast cancer revealed that there was a significant increase in apoptosis but no change in proliferation (Ki-67) in tumors exposed to trastuzumab for 1 week and that

cases with low PTEN or PI3KCA mutations were significantly less likely to achieve a pathologic CR to trastuzumab.⁷¹ Conversely, lapatinib treatment did not promote significant increase in apoptosis but did promote a significant decrease in proliferation. In addition, low PTEN or PI3KCA mutations were not associated with pathologic resistance to lapatinib, which might explain the clinical efficacy of lapatinib in some patients with trastuzumab-resistant disease.

Cell Cycle

The CDK inhibitor p27 is involved in regulating cell proliferation. p27 is a distal downstream effector of multiple converging growth factor receptor pathways, including EGFR, HER2, and IGF-1R. Trastuzumab increases the half-life of p27 by decreasing cyclin E/CDK2-mediated phosphorylation of p27 and blocking subsequent p27 ubiquitin-dependent degradation.⁷² Trastuzumab also increases association between p27 and CDK2 complexes, resulting in G₁ arrest.¹⁷ Nahta et al demonstrated that HER2-overexpressing, trastuzumab-resistant cells have low p27 levels, low p27/CDK2 complexes, and, thus, increased CDK2 activity and proliferation rate.⁷³ By flow cytometry, trastuzumab-resistant cells were found to have an increased S phase fraction and reduced doubling time. When p27 levels and CDK2 kinase activity were examined in trastuzumab-resistant cells, the investigators found that p27 was reduced irrespective of the increase in S phase and that CDK2 kinase activity was increased. Upon forcing p27 expression in trastuzumab-resistant cells via transfection or pharmacologic induction with a proteasome inhibitor, they demonstrated that trastuzumab sensitivity was restored. These data suggest that a threshold level of CDK2-associated p27 is important for the antitumor effect of trastuzumab.

Consistent with data that implicate Akt in p27 regulation, Yakes et al demonstrated that Akt inhibition is at least partially responsible for the changes in cell-cycle- and apoptosis-regulatory molecules after HER2 blockade with trastuzumab.⁶⁷ Interestingly, Kute et al demonstrated that trastuzumab activation of Akt is downregulated even in trastuzumab-resistant clones of breast cancer cells, finding that there is a lower basal association of p27 with CDK2 in trastuzumab-resistant cells compared with trastuzumab-sensitive cells and that the addition of trastuzumab did not affect the p27/CDK2 association in resistant cells.⁷⁴ Hence, resistance to trastuzumab appears to correlate with either low levels and/or cytosolic localization of p27.

Heat-shock protein (HSP) 90 is a molecular chaperone required for the stability and function of several conditionally activated and/or expressed signaling proteins.⁷⁵ HER2 is among the most sensitive client proteins of HSP90, demonstrating degradation within 2 hours of HSP90 inhibition in cell culture experiments.⁷⁶ Geldanamycin analogues (17-allylamino-17-demethoxygeldanamycin and 17-dimethylaminoethylamino-17-demethoxygeldanamycin) have demonstrated potent inhibition of HSP90 function in HER2-overexpressing cell lines, demonstrating significant antitumor activity in both cell culture and animal studies.^{76,77} In the clinical setting, initial studies of the HSP90 inhibitor tanespimycin (KOS-953)⁷⁸ and the second-generation HSP90 inhibitor alvespimycin (KOS-1022)⁷⁹ have demonstrated antitumor activity and tolerability in combination with trastuzumab in patients with trastuzumab-refractory, HER2-overexpressing MBC.

Antiangiogenesis

Over the past 2 decades, substantial laboratory and indirect clinical evidence has accumulated to support the central role of angiogenesis in breast cancer progression.⁸⁰ HER2 overexpression has been associated with increased VEGF production in breast cancers.^{19,81–84} There is preclinical and clinical rationale to support the combination of bevacizumab with trastuzumab. Treatment of breast cancer cells with the HER2 antibody

4D5 reduces VEGF production,¹⁹ suggesting that HER2 is causally associated with expression and secretion of the angiogenic factor. In addition, exposure to trastuzumab significantly decreases VEGF in HER2-overexpressing cells.⁸⁵ Comparison of all HER receptor combinations in transfected cells has shown that EGFR/HER2 and HER2/HER3 heterodimers are the most potent inducers of VEGF messenger RNA expression in vivo.⁸⁶ In vivo experiments have demonstrated a reduction in xenograft volume with the combination of trastuzumab and bevacizumab compared with a single-agent control.⁸⁵ In a cohort of 611 patients with primary breast cancer at a median follow-up of > 50 months, there was a significant positive association between HER2 and VEGF expression.⁸¹

Bevacizumab has been combined with trastuzumab in a phase I/II trial as first-line therapy for HER2-overexpressing MBC.^{87,88} An interim analysis of the first 37 patients enrolled in this trial demonstrated an ORR of 54%.⁸⁸ In the 37 patients, 13 cardiac adverse events were reported; all were grade 1/2 and asymptomatic except 1, which was a case of grade 3 left ventricular systolic dysfunction (florid congestive heart failure). Accrual of 50 patients has been completed, but a final efficacy analysis is not yet available. The phase III Eastern Cooperative Oncology Group E1105 trial, recently opened to accrual, is randomizing women with untreated HER2-overexpressing MBC to receive paclitaxel, carboplatin (optional), and trastuzumab, with or without bevacizumab, to determine the additional benefit derived from bevacizumab. The investigators will also conduct correlative studies to determine which patients are most likely to respond. Because most women with HER2-overexpressing metastatic disease receive trastuzumab in the adjuvant setting and might have disease that is relatively resistant to trastuzumab, understanding ways in which to improve response and potentially counteract resistance will be essential.

Endocrine Resistance

Epidermal growth factor receptor and/or HER2 (ErbB) receptors become important for the tumor cell at the time of escape from hormone deprivation. Preclinical models and some clinical observations suggest that ER-positive breast cancers initially inhibited by a selective estrogen receptor modulator (SERM) can use autocrine ErbB signaling in order to escape the action of the SERM.^{89–92} This mechanism involves cross-talk between growth factor signaling pathways and ER. Consistent with these observations, patients with ER-positive MBC treated with letrozole or tamoxifen who convert to HER2 positivity in their serum at the time of disease progression exhibit a shorter survival compared with those who do not convert.⁹³ Preliminary analyses of patients enrolled in BIG 1–98 and Arimidex®, Tamoxifen, Alone or in Combination (ATAC), 2 large randomized trials of adjuvant endocrine therapy in ER-positive breast cancers in which AIs and tamoxifen were used, has shown superior disease-free survival in the patients with ER-positive/HER2-negative disease compared with those with ER-positive/HER2-overexpressing disease.^{94,95} Ellis et al reported the effect of neoadjuvant endocrine therapy in postmenopausal patients with stage II/III breast cancer who were not candidates for breast conservation.⁹⁶ The clinical response after 4 months of neoadjuvant therapy with letrozole or tamoxifen was no different between the patients with ER-positive/HER2-negative disease and those with ER-positive/HER2-overexpressing disease. However, the patients with ER-positive/HER2-overexpressing disease did not show suppression of tumor cell proliferation as measured by Ki-67 IHC in the surgical specimen, suggesting continuous growth despite endocrine therapy.

The randomized phase III TAnDEM (Trastuzumab in Dual HER2 ER-Positive Metastatic Breast Cancer) study was conducted to evaluate the efficacy of trastuzumab plus anastrozole compared with anastrozole alone in postmenopausal women with HER2-overexpressing/ER-positive and/or PgR-positive MBC.⁹⁷ Median PFS was 4.8 months in the trastuzumab/anastrozole arm and 2.4 months in the anastrozole arm ($P = .0016$). The patients in the combination arm had significant improvement in ORR and CBR compared with those in the

anastrozole arm. Median survival was not statistically different between both arms of the study, although this comparison was questionable because 70% of the patients in the anastrozole arm were treated with trastuzumab at the time of progression. This trial illustrates that HER2-overexpressing/ER-positive and/or PgR-positive breast cancers are resistant to endocrine therapy in the absence of HER2 blockade.

A large randomized, double-blind, placebo-controlled, multicenter study comparing letrozole/lapatinib to letrozole/placebo in the first-line treatment of postmenopausal hormone receptor–positive (ER-positive and/or PgR-positive) MBC (EGF30008) recently completed accrual.⁹⁸ This trial accrued 1286 women with ER-positive MBC, 219 of whom also had HER2-overexpressing tumors. One third of the patients had developed metastatic disease < 6 months from receiving adjuvant tamoxifen. Median PFS in the HER2-overexpressing subgroup of patients was significantly increased in the combination arm compared to the placebo arm (8.2 months vs. 3 months). The RR and the CBR were also superior in the combination arm. Overall, no PFS advantage was seen in the HER2-negative subgroup of patients, but interestingly, a 23% reduction in progressive disease was seen in the HER2-negative group of patients who developed metastatic disease < 6 months from receiving adjuvant tamoxifen. This trial suggests that combined endocrine and targeted EGFR/HER2 inhibition enhances endocrine responsiveness in hormone-sensitive breast cancers and confirms ErbB signaling as an important mechanism of resistance to endocrine therapy. In accordance with these data, Cancer and Leukemia Group B (CALGB) is conducting a randomized study (CALGB 40302) of fulvestrant with or without lapatinib in patients with ER-positive MBC who have received previous therapy with 1 or 2 endocrine treatments for breast cancer in either the adjuvant or metastatic settings.

Practice Recommendations

From a patient management point of view, considering the standard of care treatment landscape at this time, it would be fair to consider treatment choices in the metastatic setting based on previous exposure and response to adjuvant trastuzumab. Two distinct groups of patients would stem from this classification: trastuzumab-sensitive patients (patients with no previous trastuzumab or a relapse-free interval of more than 6–12 months since the end of adjuvant trastuzumab), and trastuzumab-refractory patients (patients who progress on trastuzumab or within 6–12 months of receiving adjuvant trastuzumab).

Management of Trastuzumab-Sensitive Patients

For patients with ER-positive disease without visceral crisis who have received no prior trastuzumab or who had a modest relapse-free interval (> 6–12 months) since the end of adjuvant trastuzumab, it is reasonable to consider a combination of endocrine therapy and trastuzumab (akin to the TAnDEM trial⁹⁷) or lapatinib (based on the EGF30008 trial⁹⁸). In patients with ER-negative disease, or in those who have exhausted endocrine therapy, and especially in patients who have not received prior trastuzumab, trastuzumab without or with chemotherapy (preferred in patients with symptoms or visceral crisis) should be considered. Nevertheless, several clinical trials addressing the combination of first-line trastuzumab with other anti-HER2 therapies (such as lapatinib), PI3K/Akt pathway inhibitors, cell-cycle regulators, IGF-1 inhibitors, or antiangiogenic agents are under way in order to develop options for preventing or counteracting adjuvant trastuzumab resistance. Hence, strong consideration for early trial participation should be sought.

Management of Trastuzumab-Refractory Patients

For patients who have progressed on trastuzumab in the adjuvant or metastatic settings or within 6–12 months of receiving adjuvant trastuzumab, lapatinib without chemotherapy

(oligosymptomatic patients, low burden of disease) or with chemotherapy, endocrine therapy (for ER-positive disease), or trastuzumab should be considered. Once more, clinical trials combining trastuzumab or lapatinib with PI3K/Akt pathway inhibitors, IGF-1 inhibitors, MEK inhibitors, cell-cycle regulators, HSP90 inhibitors, or antiangiogenic agents in second-line treatment and beyond should be strongly considered. Given the plethora of agents currently being examined in clinical trials, the development of a reliable molecular signature of pathway dependence (aside from HER2) would be desirable, if available, for prioritization of clinical trial choices in subsequent lines of treatment. Optimal therapy for HER2-overexpressing MBC that is refractory to multiple lines of trastuzumab- or lapatinib-containing chemotherapy has not been established, but other novel anti-HER2 therapies, such as T-DM1 and neratinib, seem to be promising in this heavily pretreated setting.

Conclusion

Lately, the development of new strategies for the treatment of breast cancer has focused on extensive target identification and understanding the expression, regulation, and function of critical signaling pathways involved in breast cancer initiation and progression. This has led to significant progress in developing and understanding HER2-targeted therapies, which in turn has translated into a significant increase in median survival for patients with HER2-overexpressing MBC.

In the case of treatment targeted against HER2-overexpressing breast cancers, there are no biomarkers reliably predicting lack of benefit from trastuzumab that can be used for either clinical trial development or individual therapeutic decisions. Although many drugs (such as PI3K/Akt pathway inhibitors, antiangiogenic agents, cell-cycle regulators, and IGF-1 inhibitors) might be rationally combined with trastuzumab or any other HER2 inhibitor, we do not have a formal process that allows prioritization or triaging of those combinations in a way that will accelerate the approval of the most effective ones. In addition, we have no experimental models with which we can predict preferential mechanisms of escape from anti-HER2 therapy, nor do we have any data on structural alterations in HER2 or additional genetic alterations in HER2-overexpressing tumors once escape from primary anti-HER2 therapy occurs. Ideally, a biomarker profile should be developed before or during early phases of drug development in order to select patients for single-agent or combination therapies. This enforces the argument for re-biopsy of HER2-overexpressing accessible tumor tissues that escape anti-HER2 therapy after an initial response.

The study of biomarkers of drug exposure and sensitivity in metastatic tumors, although feasible, is not easy because of the inherent difficulty of obtaining sequential tumor samples only for research purposes. Reliable intermediate endpoints that allow for more rapid evaluation of the potential benefit from and the prioritization of combination therapies would be most valuable. One approach to circumvent this difficulty consists in the administration of novel therapies for patients with untreated operable cancer before definitive surgery (neoadjuvant setting). Presurgical targeted-development clinical trials that focus on extensive agent characterization and target-assay development in a limited number of patients could yield results that would optimally inform and expedite subsequent development and approval of molecularly targeted agents, providing a platform for prioritization of novel combinations.⁹⁹ The routine availability of predictive pharmacodynamic markers for early/presurgical clinical trials could provide the basis for a new paradigm in oncology.

Acknowledgments

Supported by the BCRF-AACR Grant for Translational Research in Breast Cancer and the Breast Cancer Specialized Program of Research Excellence (SPORE) grant 2P50 CA098131-06.

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