Editorial

Dual HER2-targeting without chemotherapy and estrogen deprivation in the neoadjuvant setting

William M. Sikov

Alpert Medical School of Brown University, Providence, Rhode Island, USA

Correspondence to: William M. Sikov, MD, FACP, Associate Professor of Medicine. Alpert Medical School of Brown University, Providence, Rhode Island, USA. Email: wsikov@aol.com.

Abstract: Trastuzumab has had a major impact on outcomes in HER2-positive breast cancer, but innate or acquired resistance to it is recognized as a problem that can limit its effectiveness. Given its locus of action, the oral tyrosine kinase inhibitor lapatinib would be expected to counteract many of the proposed mechanisms of trastuzumab resistance. It has demonstrated activity in trastuzumab-resistant patients, and neoadjuvant studies in HER2+ patients have demonstrated higher pathologic complete response (pCR) rates with the addition of lapatinib to trastuzumab and chemotherapy. TBCRC006 was a phase II neoadjuvant trial that studied the efficacy of the lapatinib and trastuzumab combination without concurrent chemotherapy, but with estrogen deprivation therapy in ER+ patients. In 65 patients with T2-3 HER2+ cancers, the overall pCR rate was 27%, including 36% in ER- tumors. A total 54% of ER+/HER2+ patients had either a pCR or were downstaged to T <1 cm. Correlative studies on tissue obtained prior to and during neoadjuvant therapy are underway. These results suggest that a significant fraction of HER2+ patients will respond to dual HER2-targeted therapy without cytotoxic chemotherapy, and that antihormonal therapy to block ER/HER2 'crosstalk' may be necessary to achieve optimal responses in ER+/HER2+ patients.

Keywords: HER2-positive breast cancer; neoadjuvant therapy; lapatinib; trastuzumab

Submitted Sep 02, 2013. Accepted for publication Sep 03, 2013.
doi: 10.3978/j.issn.2227-684X.2013.09.01
Scan to your mobile device or view this article at: http://www.glandsurgery.org/article/view/3042/4282

Demonstration that HER2 gene amplification is an important prognostic factor in women with both early stage and advanced breast cancer and the subsequent development of the HER2-targeted monoclonal antibody trastuzumab to block the adverse biologic sequelae of that genetic alteration were giant steps forward in the management of the 20-25% of breast cancer patients with this finding (1). However, innate or acquired resistance to the inhibiting effects of trastuzumab, even when combined with chemotherapy, is common, as evidenced by the failure of this therapy to cure patients with advanced HER2-positive (HER2+) cancers and the fraction of patients with early stage HER2+ disease who relapse despite trastuzumab-containing adjuvant therapy. A number of non-mutually exclusive mechanisms have been proposed for this resistance, including the formation of heterodimers between HER2 and other members of the HER-gene family, particularly HER3 (2), the presence of a truncated form of the HER2-receptor that is missing the extracellular domain and thus cannot be inhibited by trastuzumab, referred to as p95 (3), cross-activation of HER2-assocated signaling pathways such as the phosphoinositide kinase-3 (PI3K)/AKT/mTOR pathway by HER1 (EGFR) (4) and cross-talk between estrogen receptor (ER)- and HER2-associated pathways in HER2+ patients whose cancer cells co-express ER (5). The second generation HER2-targeted therapies, such as lapatinib and pertuzumab, counteract one or more of these resistance mechanisms; while none has proven by itself to be more effective than trastuzumab, they appear to have additive or synergistic antitumor efficacy when added to trastuzumab (6-9).

The neoadjuvant setting is useful for demonstrating

enhanced antitumor efficacy, particularly in more aggressive cancers such as HER2+ breast cancer. In such cancers, achievement of a pathologic complete response (pCR), as a surrogate for eradication of occult metastatic disease, correlates with significant improvements in recurrence-free and overall survival (10). While not well studied in this patient subset, achievement of minimal residual disease is likely also predictive of a favorable prognosis compared to patients with gross residual disease in the breast and axillary nodes, sometimes referred to as Residual Cancer Burden (RCB) (11). Single agent trastuzumab rarely induces pCR in HER2+ patients, but a much larger impact is seen with the addition of trastuzumab to neoadjuvant chemotherapy (12-14). However, even with this combination, only about half of HER2+ patients achieve a pCR, with lower pCR rates typically reported for the ER+/HER2+ cohort; for example, in the recently reported ACOSOG Z1041 trial, the overall pCR (breast) rate was 55%, but only 41% in ER+ patients compared to 75% in ER- patients (15).

TBCRC 006, as reported by Rimawi and colleagues in the May 10, 2013 edition of the *Journal of Clinical Oncology*, was a single-arm, phase II study that tested the combination of lapatinib and trastuzumab over 12 weeks as neoadjuvant therapy in HER2+ patients with tumors >3 cm in diameter, or >2 cm in patients with clinical nodal involvement (16). It is distinguished by the absence of concurrent chemotherapy and the addition of estrogen deprivation therapy in the form of the aromatase inhibitor letrozole, as well as the LHRH analog goserelin in premenopausal women, in patients with ER+/HER2+ tumors. By binding to the tyrosine kinase site in the intracellular domains of both HER1 (EGFR) and HER2 lapatinib blocks their ability to initiate the signal transduction cascade associated with the malignant phenotype; it could also be expected to block constitutive signaling by the truncated p95 HER2 receptor, if present. Among the 65 patients who initiated therapy, 62% had tumors >5 cm, 62% were ER+, 64% were premenopausal, and 54% were either African-American or Hispanic. The authors do not report the percentage of patients who were clinically node-positive, nor whether any of the patients had fixed (T4) or inflammatory cancers. As might be expected in patients not receiving standard cytotoxic therapy, treatment was well tolerated; common toxicities included grade 1-2 diarrhea, rash and fatigue, all likely due to lapatinib, but grade 3-4 toxicities were essentially limited to a few patients with transaminase elevations. The study's primary endpoint was pCR, defined as the absence of residual invasive disease in the breast. A total of 27% of patients achieved this endpoint—36% in ER- and 21% in ER+—with another 33% of the ER+ and just 4% of the ER- patients found to have residual invasive tumors ≤1 cm. Applying the more widely used criteria for pCR—the absence of invasive disease in both the breast and the axilla—reduced the rate to 22%. They do not break down the pCR or T1a/b rates in the ER+ cohort by menopausal status.

While the pCR rates reported from this study are low compared to those from studies in which patients received concurrent chemotherapy and HER2-targeted therapy, they raise hopes that, with dual HER2-targeted therapy, and the addition of estrogen deprivation therapy in ER+/HER2+ patients a subset of HER2+ patients who could have an excellent prognosis without being exposed to the short-term toxicities and long-term risks of cytotoxic therapy. A number of randomized studies have investigated the impact of adding either lapatinib (NeoALTTO, NSABP B-41, CALGB 40601) (17-19) or pertuzumab (NeoSphere) (20) to combinations of neoadjuvant chemotherapy and trastuzumab. All demonstrated an increase in the pCR rate with dual HER2-targeted therapy, though only in NeoALTTO and NeoSphere did the difference reach statistical significance. None of these studies administered estrogen deprivation therapy to ER+/HER2+ patients, and all displayed inferior pCR rates in their ER+ cohort. Also, only TBCRC006 and one arm of NeoSphere evaluated dual HER2-targeted therapy without concurrent chemotherapy; in NeoSphere, 17% of 107 patients treated with trastuzumab and pertuzumab alone for 12 weeks achieved pCR in the breast, but only 6% of ER+ compared to 27% of ER-.

Studies in patients with advanced ER+/HER2+ cancer have demonstrated the benefit of adding HER2-targeted therapy to endocrine therapies as measured by response and clinical benefit rates, time to progression and even survival (21,22). While there have been no randomized studies of the addition of endocrine therapy to HER2-targeted therapy without chemotherapy in ER+/HER2+ (sometimes called 'double-positive') patients, higher response rates in the combination arms of these studies than those reported from studies of single agent trastuzumab or lapatinib suggest a benefit to blocking ER/HER2 'crosstalk'.

In the TCBRC 006 study, while the discrepancy in pCR rates between ER+ and ER- persisted, the percentage of ER+ who patients either achieved a pCR or were downstaged to T1a-b is much higher. This supports the hypothesis that blocking the ER pathway may be important for achieving optimal response in double-positive patients.

This hypothesis will be tested in a planned NSABP neoadjuvant study, NSABP B-52, in which ER+/HER2+ patients will receive docetaxel, carboplatin, trastuzumab and pertuzumab, and be randomized as to whether they also receive estrogen deprivation therapy.

However, even with dual HER2-blockade and chemotherapy or endocrine therapy many HER2+ patients, ER- or ER+, do not achieve a pCR with neoadjuvant therapy. Part of the problem is the heterogeneity of tumors currently classified as HER2+, which likely includes cancers that are truly HER2-dependent and others with overexpression of HER2 but in which blocking HER2-associated pathways may be unnecessary; a more consistent and biologically accurate definition of HER2-positivity needs to be developed. This is illustrated by the preliminary results of intrinsic subtype analysis of pretreatment tumor samples from patients enrolled on CALGB 40601 (19). Thus far, only 33% of the study's HER2+ tumors would be classified as HER2-enriched; in contrast 55% were either luminal A or luminal B, 7% basal-like and 5% 'normal-like'. In the ER+ cohort only 18% were classified as HER2-enriched, while 77% were luminal. Preliminary analysis of pCR rates by subtype suggest that HER2-enriched cancers were much more likely to achieve a pCR with the combination of HER2-targated therapy (either lapatinib, trastuzumab or both) with weekly paclitaxel than the non-HER2-enriched subtypes. Fortunately, the TBCRC006 researchers had the foresight to collect tissue samples at baseline, week 2, week 8 and at surgery (when residual tumor was present); we await their analysis of predictive factors for optimal response to their biologics-only (including estrogen deprivation therapy for ER+ tumors) regimen.

The treatment of HER2+ breast cancer has advanced considerably over the last 20 years, and it is certain that treatment will continue to evolve as new agents, such as ado-trastuzumab, more potent tyrosine kinase inhibitors, and agents that target the signaling pathways activated by HER2 and other members of its family, are studied, and our understanding of what determines response or resistance to HER2 blockade advances. Along with the other studies of dual HER2-targeted therapies in the neoadjuvant setting, the TCBRC 006 study suggests a way forward, particularly for ER+/HER2+ patients. It must be pointed out that none of these studies have yet demonstrated improvements in recurrence-free or overall survival, and thus cannot be considered to have changed the standard of care for HER2+ patients treated in the neoadjuvant or adjuvant settings. They will have much greater impact on the treatment of HER2+ cancers if correlative studies can identify biologically meaningful subsets and these results translated into larger, more definitive trials.

Acknowledgements

Disclosure: The author declares no conflict of interest.

References

1. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-92.
2. Lee-Hoeflich ST, Crocker L, Yao E, et al. A central role for HER3 in HER2-amplified breast cancer: implications for targeted therapy. Cancer Res 2008;68:5878-87.
3. Sperinde J, Jin X, Banerjee J, et al. Quantitation of p95HER2 in paraffin sections by using a p95-specific antibody and correlation with outcome in a cohort of trastuzumab-treated breast cancer patients. Clin Cancer Res 2010;16:4226-35.
4. Ritter CA, Perez-Torres M, Rinehart C, et al. Human breast cancer cells selected for resistance to trastuzumab in vivo overexpress epidermal growth factor receptor and ErbB ligands and remain dependent on the ErbB receptor network. Clin Cancer Res 2007;13:4909-19.
5. Wang YC, Morrison G, Gillihan R, et al. Different mechanisms for resistance to trastuzumab versus lapatinib in HER2-positive breast cancers--role of estrogen receptor and HER2 reactivation. Breast Cancer Res 2011;13:R121.
6. Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 2010;28:1124-30.
7. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a German Breast Group 26/Breast International Group 03-05 study. J Clin Oncol 2009;27:1999-2006.
8. Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. J Clin Oncol 2010;28:1138-44.
9. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N

Engl J Med 2012;366:109-19.
10. Cortazar P, Zhang L, Untch M, et al. Meta-analysis results from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC). Cancer Res 2012;72:93s.
11. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol 2007;25:4414-22.
12. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005;23:3676-85.
13. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010;375:377-84.
14. Petrelli F, Borgonovo K, Cabiddu M, et al. Neoadjuvant chemotherapy and concomitant trastuzumab in breast cancer: a pooled analysis of two randomized trials. Anticancer Drugs 2011;22:128-35.
15. Buzdar A, Suman VJ, Meric-Bernstam F, et al. ACOSOG Z1041 (Alliance): Definitive analysis of randomized neoadjuvant trial comparing FEC followed by paclitaxel plus trastuzumab (FEC => P+T) with paclitaxel plus trastuzumab followed by FEC plus trastuzumab (P+T => FEC+T) in HER2+ operable breast cancer. J Clin Oncol 2013;31:abstr 502.
16. Rimawi MF, Mayer IA, Forero A, et al. Multicenter phase II study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with human epidermal growth factor receptor 2-overexpressing breast cancer: TBCRC 006. J Clin Oncol 2013;31:1726-31.
17. Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet 2012;379:633-40.
18. Robidoux A, Tang G, Rastogi P, et al. Evaluation of lapatinib as a component of neoadjuvant therapy for HER2+ operable breast cancer: NSABP protocol B-41. J Clin Oncol 2012;30:abstr LBA506.
19. Carey LA, Berry DA, Ollila D, et al. Clinical and translational results of CALGB 40601: a neoadjuvant phase III trial of weekly paclitaxel and trastuzumab with or without lapatinib for HER2-positive breast cancer. J Clin Oncol 2013;31:abstr 500.
20. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25-32.
21. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol 2009;27:5529-37.
22. Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol 2009;27:5538-46.

Cite this article as: Sikov WM. Dual HER2-targeting without chemotherapy and estrogen deprivation in the neoadjuvant setting. Gland Surgery 2014;3(1):81-84. doi: 10.3978/j.issn.2227-684X.2013.09.01

