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EDITORIAL

Making Sense of Dual HER2-Targeting in Early Breast Cancer?

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Human epidermal growth factor receptor 2 (HER2)–positive breast cancer has become one of the most treatable forms of the disease, with four FDA-approved anti-HER2 therapies (trastuzumab, lapatinib, pertuzumab, and trastuzumab emtansine) and multiple options for combining and sequencing these drugs in the metastatic setting. Dual HER2 targeting using the small molecule HER1/HER2 inhibitor lapatinib or the HER2 heterodimerization domain monoclonal antibody pertuzumab added to the anti-HER2 antibody trastuzumab improves overall survival compared with HER2 targeting using any single agent in the metastatic setting (1,2). A similar role of dual-agent HER2 targeting in preventing relapses in nonmetastatic HER2-positive breast cancer is the objective of several clinical trials in the nonmetastatic setting.

Given the expense, size, and time required for adjuvant trials, it is increasingly popular to use the neoadjuvant approach, in which the same drugs are given preoperatively and response is measured by pathologic complete response (pCR) to therapy as an intermediate biomarker for relapse-free and overall survival. This approach is justified by the unequivocal relationship of pCR to outcome (3) and is the reason that the US Food and Drug Administration (FDA) has endorsed neoadjuvant trials for registrational strategies. In 2012, the FDA granted accelerated approval of pertuzumab added to neoadjuvant chemotherapy plus trastuzumab based on a neoadjuvant trial demonstrating statistically significantly increased pCR, NeoSPHERE (4); this approval subsequently resulted in the National Comprehensive Cancer Network endorsement of pertuzumab in the adjuvant setting and incorporation of this approach in clinical practice today.

However, it is increasingly clear that improvements in pCR do not always translate into similar improvements in outcome. A highly publicized randomized neoadjuvant trial, NeoALTTO, incorporating the small molecule HER1/HER2 inhibitor lapatinib into a chemotherapy plus trastuzumab–based regimen demonstrated a statistically significant increase in pCR (5); however, the analogous adjuvant trial, ALTTO, was recently reported as negative (6). In truth, two other large randomized neoadjuvant trials, CALGB 40601 and NSABP B-41, suggested a modest impact of adding lapatinib that did not reach statistical significance (7,8) and predicted the negative ALTTO result. Working out these controversies is important, because we must have better tools for interpreting and applying results of the neoadjuvant trials that are increasingly being used in drug development and regimen optimization.

The article published in this issue of the Journal by Nagayama and colleagues illuminates these issues by examining the dual– vs single–HER2-targeting neoadjuvant question using a network meta-analysis methodology applied to randomized controlled trial data (9). Traditional meta-analysis methods are restricted to direct comparisons and are unable to draw inferences across multiple treatment regimens unless they are present in all of the studies (10). Network meta-analysis is a technique that allows both analysis of direct comparisons (regimen A vs B) and indirect comparisons (regimen A vs B derived from trials comparing A vs C and B vs C) and has become a popular means of evaluating a series of treatment regimens (11).

First, the investigators conducted a rigorous screen of the published literature under Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and identified 10 randomized studies with a total of 2247 participants, in which patients were randomly assigned to chemotherapy and/or single or dual targeting with trastuzumab, lapatinib, or pertuzumab. A total of seven treatment regimens were evaluated across the studies, the majority of which contained chemotherapy (6), or at least one HER2-targeting agent (6). The major findings from both the direct and indirect analyses were consistent with the gestalt regarding dual therapy with lapatinib and pertuzumab—both are inferior to trastuzumab as single agents, both augment pCR when added into trastuzumab-based regimens, none induces substantial acute cardiac damage, and lapatinib is more toxic than the other drugs. Their analyses also suggest that dual targeting with pertuzumab has similar effectiveness as dual targeting with lapatinib. Specifically, they found that regimens including trastuzumab+pertuzumab had an odds ratio (OR) of 2.29 (95% CI = 1.02 to 5.02), and those that included trastuzumab+lapatinib had an OR of 2.08 (95% CI = 1.18 to 3.56), compared with regimens that included only single-agent trastuzumab. Conversely, in the indirect comparison of the two dual-agent arms, no statistically significant difference was seen between adding pertuzumab or adding lapatinib (OR = 1.11, 95% CI = 0.42 to 2.86). This last finding is the only controversial and worrisome one, because it suggests that, just as the addition of lapatinib failed to improve survival in ALTTO, the similar large adjuvant trial testing pertuzumab in this setting, APHINITY, may also be negative.

This network meta-analysis has limitations. First, it includes a small number of trials—comparison of dual therapy with lapatinib is based on two trials (NeoALTTO and CHER-LOB), where a total of 198 patients were randomly assigned to the regimen, and the pertuzumab analysis is based on 107 patients treated with dual targeting on a single trial, NeoSPHERE. Unfortunately, because it limited the search to studies reported prior to August 2012, this analysis omitted two of the larger randomized trials evaluating dual

lapatinib therapy, NSABP B-41 (8) and CALGB 40601 (7). Both of these studies, which totaled nearly 600 randomized patients, found a far lower and non–statistically significant impact of lapatinib on pCR and would almost certainly have changed the odds ratios of those comparisons in this meta-analysis. Second, it is increasingly clear that HER2 as a single biomarker is probably inadequate and that subsets within HER2-positive disease, such as those that are also hormone receptor-negative (5,12,13), benefit more from additional HER2-targeting. Treatment response varies by intrinsic subtype. All the molecular subtypes can be found in HER2-positive disease (14); thus, this is a highly heterogeneous group. In addition, the gene expression array–identified HER2-enriched molecular subtype has a two-fold higher pCR rate than any HER2-targeted regimen compared with the other intrinsic subtypes (12). This means that a focus purely on drug regimens will miss important biology that affects response to any regimen. This impact of tumor biology on response may explain the variability in the results of the lapatinib trials and poses a challenge for future trial design.

Neoadjuvant trials are smaller, and thus more prone to error, and are underpowered for the clinically relevant endpoints of relapse and survival. Pooled analyses such as the effort by Nagayama and colleagues (9) can help reduce noise and provide better estimates of treatment effects. In the meta-analysis by Cortazar and colleagues (3), only one trial with a very large treatment effect, NOAH, which tested trastuzumab added to chemotherapy in HER2-positive disease, itself also demonstrated improved relapse-free and overall survival in the trial cohort with trastuzumab. Our challenge now is to determine if there is a quantitative relationship between improvement in pCR and better long-term outcomes so that these trials can be used in lieu of, rather than in addition to, large adjuvant trials. If we cannot identify such a relationship, then the clinical value of neoadjuvant trials is lost in terms of predicting survival endpoints; their value will only be in the opportunity for tissue-based studies, important academically but of limited clinical usefulness.

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Note

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