

CCR 20th Anniversary Commentary: Simpson's Paradox and Neoadjuvant Trials

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The research article by Carey and colleagues, published in the April 15, 2007, issue of *Clinical Cancer Research*, described the relationship between response to neoadjuvant chemotherapy and outcome by tumor subtype. Today neoadjuvant clinical trials are often designed to provide correlative data to help

identify predictive biomarkers or to focus on poor-risk patients identified by residual disease after neoadjuvant treatment. *Clin Cancer Res*; 21(18); 4027-9. ©2015 AACR.

See related article by Carey et al., *Clin Cancer Res* 2007;13(8) April 15, 2007;2329-34

Introduction

The same drugs administered neoadjuvantly or adjuvantly to breast cancer patients result in the same outcome (1, 2). However, there are two advantages to neoadjuvant therapy. First, giving the drugs preoperatively results in smaller, less invasive surgeries and reduces mastectomy rates. Second, response to therapy is associated with improved outcomes. Tumor eradication in breast and axillary lymph nodes, termed pathologic complete response (pCR), has been consistently associated with excellent survival in unselected breast cancers (3). This provides an intermediate endpoint for relapse and survival in early breast cancer, endpoints that in the adjuvant setting require trials involving thousands of patients and many years. Neoadjuvant clinical trials are a nimbler and faster mechanism to test new drugs and regimens, and also allow development of predictive tissue-based biomarkers in a way that adjuvant studies cannot. Recognizing these facts, the FDA endorsed pCR as an endpoint for registrational drug strategies in 2012 (4).

Our understanding of breast cancer heterogeneity has been evolving over decades, beginning with the recognition of the clinical characteristics and targetability of hormone receptor-positive breast cancer, through to the identification of HER2-overexpressing breast cancer and the development of anti-HER2 drugs, and more recently the demonstration of multiple intrinsic molecular subtypes of breast cancer (5) that have implications for interpretation of breast cancer risk factors, clinical characteristics, and behavior (6, 7). That this biologic heterogeneity might also affect chemotherapy responsiveness was suggested by the clinical ER and HER2 subsets of large adjuvant trials, which found that hormone receptor-negative breast cancer had greater benefit from chemotherapy advances than hormone receptor-positive (8).

The "Triple-Negative Paradox"

The article highlighted in this commentary, published in 2007, studied the relationship of neoadjuvant chemotherapy response to outcome among breast cancer subtypes defined by hormone receptors and HER2 (9). Examining 107 patients treated with neoadjuvant anthracycline/taxane-based chemotherapy, we found that hormone receptor-negative and HER2-positive breast cancer had the highest rates of pathologic responses to the same neoadjuvant chemotherapy regimen. What caught our (and others') attention was that the clinical groups with the highest pCR rates were also those with the worst prognosis. The association of pCR with good prognosis held true among all subsets. However, the biologic subsets with the highest overall pCR rates also had the highest likelihood of relapse and death among those with residual disease, resulting in a paradoxical relationship of a clinical subtype to both good treatment response and poor outcome. Patients with triple-negative (lacking hormone receptors and HER2) breast cancers represent one such subset, among whom 27% achieved pCR with conventional therapy, and none of these patients experienced a relapse. However, among the 73% with residual disease, the 4-year distant disease-free survival rate was approximately 60%. This was even more true in the HER2-positive/hormone receptor-negative subset, in whom chemotherapy alone without HER2 targeting resulted in 36% pCR rates and excellent outcomes, but those with residual disease had a 40% 4-year distant disease-free survival rate. Hormone receptor-positive breast cancer subsets seldom achieved pCR and had a better prognosis regardless of residual disease.

We had inadvertently identified a well-known statistical phenomenon called "Simpson's paradox," which describes the impact of unmeasured and causally important confounding variables on associations. Why would Navy sailors who go overboard at sea be more likely to be rescued if they are not wearing a life jacket? Because they only wear life jackets in bad weather, and the unmeasured variable (weather conditions) strongly influences the survival endpoint. Stratified analyses or stricter eligibility criteria are required to reduce or eliminate this problem; for example, within the good weather/bad weather strata, sailors are better off wearing life jackets. Our article illustrated the limitations of relating pCR to outcome in mixed populations, where pCR was a poor intermediate biomarker for hormone receptor-positive breast cancer, and where in other breast cancer subsets the presence of residual disease after

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conventional therapy is associated with such a poor prognosis that such individuals may be considered for trials of additional novel approaches. That pCR varied by intrinsic subtype and that triple-negative breast cancer with residual disease after chemotherapy had a particularly poor prognosis was similarly found by other researchers (10, 11), lending further support to consideration of these issues in developing clinical trials.

Neoadjuvant Trials Today

In the years since the triple-negative paradox article was published, neoadjuvant clinical trials have become more important, and their interpretation more complicated. With the explosion of novel therapies, the molecular subsetting of breast cancer, and the overall better outcome of early breast cancer patients, large adjuvant trials are nearly impossible to perform and cannot address the spectrum of therapeutic questions that face us. For these reasons, large cooperative clinical trial groups have developed neoadjuvant trials to address questions of the role of platinum drugs (CALGB 40603; GeparSixto), antiangiogenics (NSABP B-40, CALGB 40603; GeparQuinto), dual HER2-targeting (CALGB 40601, NeoALTO, NeoSPHERE, NSABP B-41), and dual- versus single-agent endocrine therapy (ALTERNATE). In some cases, a statistically significant pCR advantage in neoadjuvant trials has already failed to confer improved outcomes in large adjuvant trials, including adding bevacizumab in triple-negative (12) and lapatinib in HER2-positive disease (13), perhaps due to the unresolved inaccuracy of translating pCR into real outcomes. One of the characteristics of these systemic therapy trials is that they largely limit eligibility or plan stratification in defined subsets in order to focus the therapeutic question on the drugs most relevant for that subtype and minimize Simpson's paradox. An innovative trial, ISPY2 (NCT01042379), is designed to examine multiple novel agents added to chemotherapy in distinct clinical subsets in order to pick drugs for further development in larger studies by using pCR estimates in a Bayesian adaptive design. Several drugs, including neratinib in HER2-positive breast cancer and veliparib + carboplatin in triple-negative breast cancer, have already "graduated" to larger trials.

However, the association of pCR with better outcomes has not clearly resulted in a quantitative relationship that is predictable in its magnitude, and that could allow us to omit large adjuvant trials; thus, Simpson's paradox still impedes developing pCR as an intermediate endpoint. Part of the problem may be the molecular heterogeneity within all of the clinical subsets of breast cancer. Triple-negative disease comprises several biologic entities, as is HER2-positive disease and hormone receptor-positive breast cancer, and it is increasingly clear that the molecular entities within these clinical subsets are relevant for treatment response to targeted treatments. For example, thoughtful approaches to a relevant biomarker in hormone receptor-positive breast cancer include development of the Preoperative Endocrine Prognostic Index (PEPI), which predicts the likelihood of response and outcomes in hormone receptor-positive patients. PEPI scores to the same aromatase inhibition strategies differ between luminal A and luminal B subtypes (14). Clinically, HER2-positive disease mostly comprises the HER2-enriched and luminal subtypes (15); response to regimens, including HER2-targeting drugs, varies markedly across these subtypes (16, 17), although whether this remains true for survival is not yet clear. Several other factors appear to independently affect pCR rates in

HER2-positive disease, including PIK3CA and p53 mutations. Even more intriguingly, in both HER2-positive and triple-negative breast cancer, pCR and outcome are affected by the presence and/or activation status of infiltrating immune cells, suggesting a significant contribution of the tumor microenvironment to response to treatment (16, 18–20). Identifying and adjusting for these confounding variables is a challenge but also an opportunity to identify subsets of patients within poor-prognosis subtypes who may do well with less aggressive therapies.

Residual Disease Trials

Residual disease after neoadjuvant chemotherapy is a vexing issue, with little data suggesting the best course of action. Several trials leverage the other main finding of the study, namely identifying those patients who by virtue of residual disease after neoadjuvant chemotherapy are at sufficient risk of relapse as to be appropriate for novel treatments. For example, eligibility for the cooperative group trial S1207 (NCT01674140) includes patients with residual nodal involvement after neoadjuvant therapy, and A011202 (NCT01901094) compares axillary dissection to radiation in those with persistently positive sentinel nodes after neoadjuvant systemic therapy. ECOG-ACRIN (NCT02445391) randomizes patients with residual triple-negative disease after anthracycline/taxane-based neoadjuvant therapy to receive a platinum drug in the adjuvant setting, further exploring the pCR benefit seen with the addition of platinum drugs in the neoadjuvant setting (21, 22). The KATHERINE study (NCT01772472) is comparing adjuvant trastuzumab emtansine versus conventional trastuzumab in patients with residual disease after a neoadjuvant HER2-targeted regimen. The most innovative of these may be the ALTERNATE study (NCT01953588), in which patients with persistent evidence of proliferating tumors on biopsy after 4 weeks of therapy are changed from neoadjuvant endocrine therapy to chemotherapy.

Examination of the residual disease itself may also provide clues to improved therapeutic strategies. Recent studies in residual triple-negative disease found potentially targetable genomic alterations, such as alterations in PTEN, JAK2, and cyclin D family members (23), and residual disease after neoadjuvant HER2 targeting was significantly enriched for luminal A disease (16).

Conclusions

This 2007 "paradoxical" paper was part of an emerging focus on using response to neoadjuvant therapy to better define early breast cancer regimens. We highlighted the relevance of pCR to outcome as well as the complexity of translating pCR to endpoints of clinical relevance, such as relapse and survival. Since that time, it has become even more clear that therapeutic investigations in breast cancer must account for biologic heterogeneity, but also that neoadjuvant trials are key to the success of these investigations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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