Using neoadjuvant therapy for breast cancer in clinical practice: when and how?

Debu Tripathy

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The roles of neoadjuvant therapy both as a standard therapeutic approach and a research tool are very closely tied and have yielded insights into both breast cancer biology and new drug development [1, 2]. From a clinician's standpoint, however, the key questions that arise revolve around the clinical advantages of neo-adjuvant therapy in terms of surgical outcomes, long-term recurrence/mortality and decision-making. At the current time, the main advantage of neoadjuvant therapy is to improve the odds of adequate surgical resection, particularly breast-conserving surgery [3, 4]. Beyond that, long-term outcomes or clinical decision-making do not appear to be affected by the sequence of systemic therapy in relation to definitive surgery. It is becoming clear that breast cancer is heterogeneous. Genomically defined subsets, which map to some extent with hormone and HER2 receptor subtypes, exhibit differential recurrence hazard reductions with systemic therapies—and this concept also applies to neoadjuvant therapy response as well [5]. But there is also clinical diversity, for example, contrasting rapid onset inflammatory cancer to a more indolent cancer that has been clinically present for several years. Therefore, current neoadjuvant treatment paradigms must incorporate the base of evidence from large scale clinical trials as well as the biological context of the disease. The reports contained in this special issue of Breast Cancer Research and Treatment highlight current trends and results that are shaping both patient care and research in this area.

The report by Lin et al.[6] demonstrate biological differences between interval and screen-detected cancers

treated on a prospective trial, even though the number of screening-detected cancers was small, as would be typical in a neoadjuvant trial where the majority of patients were not undergoing screening. As expected, interval cancers had a tendency to be hormone receptor-negative and of higher grade, whereas screen-detected cancers were all of the luminal intrinsic subtypes by gene expression array. Nevertheless, this report points to the need to stratify patients by known characteristics associated with response in clinical trials and to use established factors in routine clinical practice. For example, it is now clear that patients with hormone receptor-positive cancer have less response to neoadjuvant therapy and lower pathologic complete response (pCR) rates. Receptor status might therefore affect the decision regarding the timing of chemotherapy, especially if breast-conserving surgery is driving the decision. Several phenotypes that are also related to hormone receptor content, but appear to have independent prognostic factors for response, such as proliferation index and risk score by gene profile assays are the next markers on the horizon that could enter into this decision-making if tumor size reduction is a main goal of therapy [7, 8].

Is there an optimum neoadjuvant regimen? Should non-standard adjuvant regimens that yield high pCR rates be adopted into routine practice? Until neoadjuvant trials are powered for long-term outcome, at the current time, it is important to remember that the most important benefit of neoadjuvant therapy is its “adjuvant” effect on long-term recurrence and mortality. Therefore, an evidence-based approach would dictate the use of proven standard adjuvant regimens in the neoadjuvant setting. However, trials that bridge pCR rates in relevant subsets to long-term outcome could serve as the basis for approvals of new drugs and regimens and eventually shorten regulatory approval times [9]. Some long-standing standards may need to be

D. Tripathy (✉)
Norris Comprehensive Cancer Center, University of Southern
California, 1441 Eastlake Avenue, # 3429, Los Angeles,
CA 90033, USA
e-mail: tripathy@usc.edu

questioned based in findings in neoadjuvant trials—for example, the use of sequential adjuvant hormonal therapy after chemotherapy as opposed to concurrent use has now become the standard based on trials using tamoxifen even these have not been definitive [10, 11]. However, concurrent use of aromatase inhibitors, which may interact with chemotherapy in a manner distinct from that of tamoxifen, has never been formally tested. One of the articles in this supplement provides support for such studies, in showing a significant increase in pCR rate with concurrent letrozole compared to chemotherapy alone, and this may raise the larger questions of concurrent hormonal and chemotherapy [12]. Newer paradigms of dual blockade of the HER2 pathway are uniformly showing benefits without much added toxicity of trastuzumab combined with pertuzumab or lapatinib although for now, these will need to be verified in prospective trial as they are testing novel agents [13, 14]. However, other questions specific the neoadjuvant setting such as the value of anthracycline versus non-anthracycline in combination trastuzumab in achieving a higher degree of response has been suggested, but may need formal testing specifically in the neoadjuvant setting where response is linked to long-term outcome [15].

This issue also contains reports of novel predictive markers such as p53 mutation status, the extent tumor infiltrating lymphocyte and the cell death pathway mediator Serpin3 [16–18]. However, markers predictive of specific agents and regimens are needed for clinical decision-making and will require further evaluation in both neoadjuvant and adjuvant trials. This is critical since early predictive biomarkers that have arisen from the laboratory are not always being confirmed in larger scale clinical trials, for example, the truncated HER2 receptor p95 that is associated with resistance to trastuzumab in laboratory models and small clinical series are not holding up when analyzed in the context of larger randomized neoadjuvant trials [19, 20]. However, clinical decision-making will require treatment-specific predictors that are validated and consistent across studies, with the recognition that some predictors or classifiers may apply to response and not metastasis and survival, and as such will need to be applied in the proper clinical context. If clinical response is the key driver for making a decision in a specific case, then the indices used for this outcome should be employed.

Among the greatest potential advantage of neoadjuvant therapy would be the use of degree of response to adjust therapy to improve long-term outcome. In the GeparTrio study, the strategy of changing chemotherapy following clinical response assessment at two cycles did not improve pCR rate, but interestingly, on longer term follow-up, there is now a disease-free survival based on response-guided therapy in non-responders [21]. These are the types of trials that hold the potential to improve outcome through the

information gained during the course of therapy. Ultimately, this approach can lead to new discovery of agents and regimens and the appropriate classifiers to optimize candidates who will benefit the most.

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