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EDITORIAL – BREAST ONCOLOGY

Neoadjuvant Chemotherapy for Breast Cancer: The Ultimate "Spy"

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The second half of the twentieth-century saw the development of chemotherapy, a medical advancement that coincided with the transition from Halstead mastectomies to less aggressive and disfiguring operations for women with breast cancer. The efficacy of cyclophosphamide, methotrexate, and fluorouracil as adjuvant treatment for breast cancer was published in 1975 and, along with reports from the National Surgical Adjuvant Breast and Bowel Project (NSABP), raised hope that chemotherapy could play a major role in the management of breast cancer.[1,2] These pivotal works introduced the concept that adjuvant chemotherapy following breast cancer surgery leads to better outcomes.

Trials of neoadjuvant chemotherapy (NAC) hypothesized that early treatment of subclinical micrometastases would improve survival. While previously used only for locally advanced cancers, NAC use was extended to include operable breast cancers and the secondary endpoints of these clinical trials assessed the response of the primary breast tumor and involved lymph nodes.[3,4] Survival benefits were not seen in these early clinical trials; however, decreased tumor size and eradication of axillary disease were noted in some patients. In this setting, NAC highlighted the heterogeneous nature of breast cancer.[5] The identification of complete eradication of disease after NAC, defined as pathologic complete response (pCR), would have profound implications.

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By the early 2000s, trials such as the Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And moLecular analysis (I-SPY1) were initiated to better categorize and understand tumor response to NAC. The multicenter I-SPY1 study sought to integrate multiple sources of data evaluating pathologic response and recurrence-free survival. It represented a more precise and personalized exploration of tumor response to chemotherapy. I-SPY1 and similar trials helped elucidate that pCR differs by receptor subset.[6]

I-SPY2 was designed to help identify therapeutic agents early in the drug development cycle that improve rates of pCR. By taking advantage of information gained during NAC and acquired as part of the study, this group sought to address the long, expensive process of oncology drug development. By radically transforming the clinical drug development process, they desired to create a more efficient and effective system that could better meet healthcare needs. The design is unique and described as a neoadjuvant, adaptively randomized, multicenter phase 2 platform trial evaluating investigational therapies with pCR as their primary endpoint. Given the novel use of pCR for drug development, the Food and Drug Administration specifically weighed in with support on its use for accelerated approval of drugs following NAC for breast cancer.[7] From trial initiation in 2010 until 2020, I-SPY2 completed evaluation of 15 investigational therapies.

Along with pCR, the I-SPY2 trial assesses residual cancer burden, event-free survival (EFS), and distant recurrence-free survival (DRFS) following NAC. In 2020, the I-SPY trial consortium published 3-year follow-up findings on the association of EFS and DRFS with pCR.[8] Patients included in this analysis had stage 2 or 3 breast cancer with tumors exceeding 2.5 cm. A 70-gene assay score was run for hormone receptor (HR) positive patients and those with a low score were excluded. A total of 1038

patients received treatment on 1 of 9 arms of therapy, including a control arm and the experimental agents individually or in combinations. Across all subtypes of this higher-risk patient population, approximately 1/3 achieved pCR following NAC. Unsurprisingly, the lowest pCR (17.4%) was observed in patients with HR-positive, ERBB2-negative tumors, and the highest pCR was observed in patients with HR-negative, ERBB2-positive tumors (68%). The trial demonstrated that regardless of subtype and/or treatment regimen, achieving pCR after NAC treatment reduced recurrence by approximately 80%. The findings in this recent, tightly controlled patient cohort suggest high correlation between pCR and clinical outcomes. The authors conclude that "these data should drive and inspire us to think about how to maximize the chance that each individual can achieve pCR." Interestingly, the article is followed by an editorial written by statisticians cautioning on the use of pCR as a surrogate endpoint for cancer clinical trials.[9]

For breast cancer providers, the implications of a pCR are paramount. Accurate assessment of the presence or absence of residual disease is important in the breast and the axilla, and the consequences of it are significant for adjuvant therapy. Both the Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) and KATHERINE trials demonstrated survival benefits with changes in therapy for patients who did not experience pCR after NAC.[10,11] An opportunity to de-escalate medical, radiation, and surgical therapy—all currently under investigation in multiple clinical trials—is possible for patients who achieve pCR.

The CompassHER2-pCR trial (also known as EA1181) is studying reduced chemotherapy using pCR to guide treatment strategy.[12] Patients with ERBB2-positive tumors receive an NAC regimen comprised of a taxane, trastuzumab, and pertuzumab. Patients who achieve pCR are dosed with trastuzumab and pertuzumab for 1 year but receive no additional chemotherapy.

Is it possible to de-escalate surgical therapy in this setting? In a large, multicenter pooled analysis, reliable prediction of pCR has been demonstrated following image-guided vacuum-assisted biopsy of a tumor bed measuring 2 cm or less from patients treated with NAC with 6 or more representative samples collected.[13] Using this information, researchers are investigating whether surgery is necessary following NAC in some cases of triple negative and ERBB2-positive breast cancers.[14] Already we have witnessed a transition from axillary lymph node dissection (ALND) to sentinel lymph node biopsy (SLNB) to establish pCR in the axilla. While many believed ALND was needed for therapeutic and diagnostic reasons, use of SLNB is deemed acceptable for assessing the axilla following NAC for node-positive disease in select cases. Evidence shows that the use of dual tracers and the removal of at least 2 nodes and any initial clipped lymph nodes can safely stage the axilla with low false negative rates.[15,16] Most clinical NAC trials accept that SLNB in this context represents an appropriate measure of residual disease in the axilla.

Establishing and identifying pCR in our patients requires meticulous evaluation of the breast and axilla by a multidisciplinary team, including radiologists, pathologists, medical oncologists, radiation oncologists, and surgeons. Achieving a pCR should be celebrated and can set the tone for positive outcomes. Importantly, it presents tremendous opportunities to guide de-escalation AND escalation regimens. The researchers and patient cohorts helping to advance this area should be commended. We must continue enrolling patients in these groundbreaking studies that have the potential to forever alter how we treat breast cancer.

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