Taking a Second Look at Neoadjuvant Endocrine Therapy for the Treatment of Early Stage Estrogen Receptor Positive Breast Cancer During the COVID-19 Outbreak

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The global COVID-19 pandemic has abruptly changed our approach to cancer care. In the face of a potentially deadly virus, surgeons must balance the risks of a delayed surgery for patients with newly diagnosed cancers with the risks of exposure to the virus in this potentially immunocompromised patient population. We must also consider the necessity of conserving limited hospital resources; effectively diverting life-saving medical care to manage a more imminent crisis. Undoubtedly, this is an unprecedented and highly unnerving time. These decisions are very challenging for physicians to make and understandably difficult for patients to accept. Several medical and surgical societies have published expedited consensus guidelines to help triage care for cancer patients.[1] For breast cancer patients with estrogen receptor (ER) positive disease, which account for approximately 75% of all breast cancers, a deviation from the current standard of care is being recommended as a safe alternative to the traditional ''surgery first'' approach.

Estrogen-blocking therapy was the first effective targeted therapy developed for breast cancer and has become the mainstay for the adjuvant treatment of patients with ER-positive disease. The use of endocrine therapy in the neoadjuvant setting, however, has been more limited. In the face of the current pandemic, multidisciplinary experts are recommending this approach as a bridge to surgery for many breast cancer patients. Considering this, it is a pertinent time to revisit the data supporting neoadjuvant endocrine therapy (NET), collect prospective data, and consider whether this imposed deviation will compel a more lasting role for NET in the treatment of ER-positive breast cancer.

Traditionally, neoadjuvant chemotherapy (NAC) has been used to downstage breast cancer: to render a nonoperable tumor resectable and to convert surgery from a mastectomy to breast conservation. Several studies demonstrate similar efficacy of chemotherapy whether given in the adjuvant or neoadjuvant setting.[2] However, the ability to evaluate for in vivo biologic treatment response has become a significant driver for the use of NAC, particularly in patients with triple negative or Human epidermal growth factor receptor 2 (HER2) over-expressed subtypes. Treatment response has both prognostic and therapeutic value. For prognostic value, patients who achieve a pathologic complete response (pCR) after NAC have improved survival compared to those who have residual disease.[3] For therapeutic value, patients who have residual disease after NAC are now candidates for additional treatment with capecitabine[4] or trastuzumab emtansine.[5] The ability to treat patients with a second line of therapy with curative intent based on individualized NAC response is a highly attractive paradigm.

For patients with ER positive breast cancer, the benefit of chemotherapy is less clear, and pCR rates after NAC are consistently lower.[3] For these reasons, NAC is not widely used for patients with ER positive breast cancer. NET has been studied as an alternative to NAC. Initial studies from Europe[6,7] and the United States[8] demonstrated that 3–4 months of NET successfully downstaged patients with ER positive breast cancer from mastectomy to breast conservation in 22%–87% of post-menopausal patients, with aromatase inhibitor (AI) therapy demonstrating greater efficacy than Tamoxifen. Similar results were noted in premenopausal patients with neoadjuvant ovarian suppression and AI therapy.[9] A subsequent meta-analysis by Spring et al[10] evaluated over 20 studies and 3500 patients and demonstrated that NET achieved similar clinical response rates to NAC, but with lower toxicity. Despite these data, the widespread adoption of NET into clinical practice has been slow.[11] This is likely due to the low rates of pCR overall with NET and the lack of prognostic significance of this endpoint in patients with ER positive disease.

Biomarker testing has emerged as a promising and rapid measure of assessing clinical response to NET for patients with ER positive breast cancer. A decrease in the proliferation marker Ki-67 from baseline after 2 weeks of therapy is a significant predictor for improved recurrence-free survival[12] and may identify patients who will do well with endocrine therapy alone. The preoperative endocrine prognostic index incorporates Ki-67 proliferative index, ER Allred score, and pathologic stage and is also a useful prognosticator, with a preoperative endocrine prognostic index score of 0 correlating with lower rates of relapse at 5 years.[6]

In patients treated with the NET approach, clinical progression is seen in 5%–20% of patients. For these patients who demonstrate early endocrine resistance to NET, this would allow consideration of alternative treatment approaches to reduce recurrence risk and progression to metastatic disease (rather than the traditional 5 years of endocrine monotherapy). Interestingly, results from the ACOSOG Z1031 trial demonstrated that switching to NAC for these endocrine ''nonresponders'' whose Ki-67 levels remained >10% did not result in increased rates of pCR.[13] Thus, for this group, chemotherapy may still not be the answer. Rather, these patients may likely benefit from new and emerging therapies for ER positive breast cancer.

Several mechanisms of acquired endocrine resistance have been described, including loss of ER expression, activating Estrogen receptor 1 (ESR-1) gene mutations,[14] and hyperactivity of cell cycle regulators.[15] Whether there is a correlation between early endocrine

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resistance (manifested by persistently elevated Ki-67) and predisposition towards these resistant pathways is worthy to explore and may provide therapeutic insight. Other strategies for overcoming endocrine resistance such as combination, alternating or sequential therapies should continue to be explored. Hurvitz et al[16] recently demonstrated that 14 days of neoadjuvant abemaciclib as monotherapy or in combination with an AI significantly suppressed Ki-67 levels over AI therapy alone. As these studies continue to evolve, agents such as CDK 4/6 inhibitors, the selective ER degrader fulvestrant, and PI3K inhibitors will likely become standard in the adjuvant setting. Importantly, response to NET may be a useful way to identify patients with ER positive breast cancer who would benefit most from these specific therapies.

Studies evaluating NET for patients with ER positive breast cancer demonstrate that this is a safe approach with low toxicity. This should provide reassurance for patients and physicians during these uncertain times. Although not cytotoxic, NET is very effective in reducing proliferative activity of breast cancer cells and inducing cell cycle arrest, so should function as an effective bridge to subsequent surgery. However, patients will need to be followed closely to ensure an appropriate response to treatment, and surgery must be considered for patients who demonstrate progression on NET.

Historically underutilized but propelled by the unprecedented need to curtail surgery, NET may yet gain a foothold in the modern management of early-stage, ER positive breast cancer. The COVID-19 pandemic, although devastating to unthinkable levels, has brought forth a unique opportunity to prospectively track outcomes of these patients as a nation to help determine the true risks and benefits of this treatment approach. Whether outcomes ultimately influence practice long-term beyond the COVID-19 pandemic or proves NET to be a crisis-induced deviation that is quickly discarded once the pandemic resolves, only time will tell.

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