Current Perspectives on Neoadjuvant Treatment of ER-Positive BC

Written by Nicola Parry

In a session on neoadjuvant treatment of patients with estrogen receptor (ER)-positive breast cancer (BC), 3 presenters reviewed its efficacy, predictive biomarkers, and clinical trials evaluating novel targeted agents.

David A. Cameron, MD, University of Edinburgh, Edinburgh, United Kingdom, provided clinical insights on the neoadjuvant therapy of ER-positive BC in postmenopausal women. Although neoadjuvant therapy has historically been chemotherapy based, Prof Cameron advocates a similar approach to that of the adjuvant setting, which focuses on avoiding chemotherapy based on cancer biology. Not all women with BC need chemotherapy, since endocrine therapy can induce effective responses.

In the P024 study, for example, letrozole therapy was more effective than tamoxifen in terms of clinical, mammography, ultrasonography, and breast conservation responses [Ellis MJ, Ma C. *Breast Cancer Res Treat.* 2007]. In the IMPACT study, which compared the efficacy of anastrozole, tamoxifen, and a combination of both, anastrozole produced the highest improvement rate for conversion to breast-conserving surgery [Smith IE et al. *J Clin Oncol.* 2005] and the highest antiproliferative effect [Dowsett M et al. *J Clin Oncol.* 2005].

Prof Cameron also emphasized the need for patience when treating ER-positive BCs because they respond more slowly to chemotherapy and endocrine therapy. A recent study showed that overall response rate (ORR; 95% vs 45%) and pathologic complete response (pCR) rate (17.5% vs 2.5%) increased in patients who received 1 year of neoadjuvant therapy, compared with 4 months [Allevi G et al. *Br J Cancer.* 2013]. In the TEAM IIa trial [Fontein DBY et al. *Eur J Cancer.* 2014], proliferation continued to decrease between 3 and 6 months of therapy, and the breast conservation rate also increased (62% vs 71%).

Although the optimal duration of neoadjuvant therapy is unknown, Prof Cameron added that the traditional 3 or 4 months' duration is suboptimal, and 5 to 10 years, as in the adjuvant setting, may be more realistic.

While pCR rates are lower with endocrine therapy and chemotherapy in ER-positive BCs, particularly those that are human epidermal growth factor receptor 2 (HER2)-negative [Cortazar P et al. *Lancet.* 2014], he stressed that pCR is not the goal of neoadjuvant therapy—it is the clinical effects and long-term patient benefits that matter.

With respect to choice of neoadjuvant therapy, Prof Cameron emphasized that the data on aromatase inhibitors clearly highlight why they have become the de facto treatment. However, he believes it is reasonable to choose the same agents as would be used in the adjuvant setting.

Mitchell Dowsett, PhD, FMedSci, Royal Marsden Hospital and Institute of Cancer Research, London, United Kingdom, discussed biomarkers in the endocrine and chemotherapy settings.

ENDOCRINE THERAPY

Endocrine therapy predominantly suppresses tumor cell proliferation without an increase in apoptosis, and this correlates with the slow response to this form of therapy, said Prof Dowsett. Data from the IMPACT study [Dowsett M et al. *Clin Cancer Res.* 2005] showed the power of Ki67 to predict treatment benefit; anastrozole produced more significant reductions in Ki67 expression, compared with tamoxifen, after 2 and 12 weeks ($P = .004$ and $P < .001$), with near-maximal responses at 2 weeks.

The degree of downregulation of proliferation also predicts treatment benefit. After 12 weeks of endocrine therapy, Ki67 levels increased in some patients after an initial decrease, suggestive

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of acquired treatment resistance [Dowsett M et al. *J Natl Cancer Inst*. 2011]. Levels initially decreased minimally in others, suggestive of de novo resistance. In the long term, these patients with acquired or de novo resistance experienced equally poor outcomes, compared with those who experienced and maintained more significant Ki67 reductions.

At the time of surgery, the proliferation rate of the residual cancer cells also predicts recurrence risk, he added.

CHEMOTHERAPY

Conversely, chemotherapy leads to decreased cellular proliferation, which may be driven by increased apoptosis. Increases in apoptosis have been shown to occur quickly—within 24 hours of primary chemotherapy [Archer CD et al. *Br J Cancer*. 2003]. Patients treated with chemotherapy typically experience rapid regressions, and the degree of cell death may predict the response to treatment, said Prof Dowsett.

The proliferation rate of residual cancer cells at surgery also predicts the risk of recurrence, with poorer outcomes associated with a higher residual cancer burden (RCB) [Symmans WF et al. *J Clin Oncol*. 2007], and high post-chemotherapy Ki67 levels [von Minckwitz G et al. *Clin Cancer Res*. 2013; Jones RL et al. *Breast Cancer Res Treat*. 2009].

Combining Ki67 with RCB to create the residual proliferative cancer burden can also enhance the prediction of long-term recurrence risk [Sheri A et al. *Ann Oncol*. 2014].

According to Ingrid A. Mayer, MD, MSCI, Vanderbilt University, Nashville, Tennessee, USA, neoadjuvant endocrine therapy trials comprise a valid alternative for patients with ER-positive BC and provide insights into the biological basis for therapeutic responses to ER-targeting agents.

She shared preclinical data on the role of different signaling pathways, such as P13K and ErbB pathways, in mediating resistance to endocrine therapy, which supported the combination of endocrine therapy with specific pathway inhibitors in an attempt to maximize efficacy and minimize therapeutic resistance.

Several examples of clinical trials in the metastatic setting were shown as a proof of concept of the clinical benefit provided by the addition of P13K/mTOR pathway inhibitors, such as BOLERO-2 [Yardley et al. *Ad Ther*. 2013], which evaluated the efficacy of combined everolimus and exemestane, and a recent phase 1b study [Mayer IA et al. *J Clin Oncol*. 2014] that investigated the combination of letrozole and the pan-phosphoinositide-3-kinase (PIK3) inhibitor buparlisib in patients with ER-positive, HER2-negative BC refractory to previous endocrine therapies.

Currently, phase II neoadjuvant trials exploring the addition of inhibitors of the P13K/AKT/mTOR pathway to endocrine therapy are underway. A phase 2 randomized trial [NCT01923168] is also currently ongoing to investigate the efficacy of letrozole with or without 1 of 2 PI3K inhibitors, BYL719 and buparlisib, in patients with mutated and wild-type *PIK3CA* gene, said Dr Mayer.

As an example of genomically driven clinical trial design platform, patients with ER-positive, HER2-negative, stage 2 or 3 BC undergo a biopsy for sequencing purposes, and the ones with a *PIK3CA* mutation will enter a trial involving the Akt inhibitor MK-2206 plus anastrozole [NCT01776008], while those without will enter a trial involving the Cdk4/6 inhibitor PD0332991plus anastrozole [NCT01723774].

Dr Mayer emphasized that neoadjuvant endocrine therapy trials also serve as discovery platforms that enhance understanding of the molecular mechanisms of resistance to estrogen deprivation. This may facilitate development of effective mechanism-based treatments for endocrine therapy-resistant disease.