



Commentary

Ovarian function suppression as a potential mechanism of chemotherapy

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Neoadjuvant chemotherapy (NAC) is occasionally considered for treatment of early-stage hormone receptor positive (HR+) breast cancer, primarily for downstaging of disease to allow for lesser aggressive surgical interventions. Classically, however, HR+ disease demonstrates a less robust response relative to HR negative (HR-) disease, although there is increasing evidence regarding benefit of chemotherapy in general for use in pre-menopausal versus postmenopausal women [1].

Pre-menopausal women with early-stage HR+ breast cancer demonstrate higher rates of achieving a pathologic complete response upon receipt of NAC, as compared to neoadjuvant endocrine therapy (NET) [2], a finding in contrast to observations made from trials evaluating responses to neoadjuvant therapy in postmenopausal patients. In CORALLEEN, post-menopausal patients with HR+ HER2-, luminal B disease received either NAC or endocrine therapy (ET) plus a CDK inhibitor. Changes in risk of recurrence from high to low risk as assessed by the Prosigna Breast Cancer Prognostic Gene Signature Assay (formerly known as PAM50 test was roughly equivalent between the groups [3]. Similarly, in SOLTI-1501 VENTANA, post-menopausal patients that received metronomic doses of vinorelbine plus letrozole did not display statistically superior anti-proliferative effects with regard to decreases in PAM50 score as compared to patients receiving letrozole only [4].

To parse the mechanism underlying the benefit of NAC in pre-menopausal women, it can be argued that there may be intrinsic gene profiles in this population that are differentially altered as a result of exposure to chemotherapy as compared to their post-menopausal counterparts. In this issue of *EBioMedicine*, Chic et al endorse this hypothesis by identifying a predominant effect of genes that are altered as a result of chemotherapy effect on ovarian suppression [5]. Utilizing gene expression data from CORALLEEN [3], VENTANA [4], PAMELA [6], NEOERIBULIN, and two retrospective cohorts from the

Hospital Clinic de Barcelona, the authors identify a panel of 19 genes – notably including PGR encoding the progesterone receptor – consistently downregulated in post-menopausal patients receiving either ET plus a CDK inhibitor or ET alone, which is not seen in post-menopausal patients receiving NAC. These findings were validated *in vitro* upon treatment of MCF7 HR+ breast cancer cells with estradiol resulting in upregulation of this gene set. Interestingly, the 19 gene panel was again found to be downregulated in patients receiving NAC. However, this effect was limited to the pre-menopausal cohort and not seen in post-menopausal women, suggesting overlap in hormone signalling pathways that are affected in post-menopausal patients receiving ET and pre-menopausal patients receiving NAC.

PGR was similarly downregulated in patients with HR+ HER2 positive (HER2+) disease treated with ET plus HER2 directed therapy, but conversely upregulated with HER2 directed monotherapy in patients with HR- disease. The authors further demonstrate that PGR downregulation in patients with HER2 disease is limited to the pre-menopausal cohort.

As implied by the authors, the benefit seen with NAC in pre-menopausal women may plausibly be due to the reduction in estrogen/progesterone receptor signalling derived from chemotherapy-induced ovarian suppression. This would be in line with prior findings demonstrating improved disease-free survival in patients receiving ovarian function suppression (OFS) added to tamoxifen after receiving NAC who remained pre-menopausal or with resumed ovarian function [2]. However, whether that induction of OFS with goserelin or other GnRH analogues is as effective as chemotherapy in the neoadjuvant setting is yet to be determined. This is even less straightforward in the case of HER2+ breast cancer based on the reported findings and ultimately will be best clarified by clinical trials in the neoadjuvant setting in which OFS is more closely studied.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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