Reviewer’s report

Title: In situ aromatase expression in primary tumor is associated with estrogen receptor expression but is not predictive of response to endocrine therapy in advanced breast cancer

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General Comments

The manuscript titled “In situ aromatase expression in primary tumor is associated with ER expression but is not predictive of response to endocrine therapy in advanced breast cancer” used semi-quantitative immunohistochemical (IHC) analysis to determine expression of ER, PR, COX-2 and aromatase in tissue samples collected from 88 patients who participated in a randomized clinical trial comparing aromatase inhibitor (AI), letrozole to anti-estrogen, tamoxifen. The study was carried out using either tissue microarrays (TMAs) for ER, PR, COX-2 and aromatase and also whole sections (WS), in case of aromatase. The author demonstrated that aromatase IHC evaluation in TMAs were too heterogeneous and not comparable to results from WS. Moreover, the author showed that aromatase expression was correlated with ER but not with PR or COX-2 expression. However, patients treated with letrozole with high PR and aromatase expression were associated with a longer time to progression (TTP).

Overall, this is a well-designed study with proper controls. The demonstration that TMAs are not suitable to evaluate the overall aromatase expression in tumor samples is important and will be beneficial in evaluating tumor aromatase expression in future studies. More importantly, the study showed that patients with high PR and aromatase expressing tumors are likely to get superior benefit from AI (letrozole) treatment.

Major Compulsory Revisions

1. Several studies showed aromatase expression in both epithelial and stromal cells. Oliverira et al, showed high positivity of aromatase expression in stroma of invasive ductal carcinoma and lower positivity in both normal and epithelial and stroma. Did the author score aromatase expression in the stromal in addition to carcinoma cells? If so, is there any correlation between stromal aromatase with ER, PR or COX-2?
Minor Essential Revisions

2. On page 14, the author mentioned that the consistencies of IHC scores on TMAs and WS for ER, PR and COX-2 expression have previously been reported. Please include the reference.

3. The authors found no significant correlation between aromatase and COX-2 or PR but found a strong correlation between aromatase and ER expression. As a positive control for this study, what is a correlation between ER and PR expression in this study?

4. As mentioned in the discussion, most studies found a positive correlation between COX-2 and aromatase expression both at transcriptional level and protein levels in invasive breast tumor tissue. However, no correlation between COX-2 and aromatase expression was found in this study. The author suggested the complex regulation of aromatase enzyme activity and different antibody used in this study. Since the result of this study is in contrast to most published studies, a thorough discussion of this particular result is needed. For example, as mentioned in #3, aromatase is not only expressed in carcinoma cells but also expressed in the surrounding stroma. Both COX-2 and aromatase expression are often influence by epithelial-stromal interaction. A discussion of epithelial-stromal interaction would be beneficial.

Discretionary Revisions

5. This study suggested that high PR and aromatase expression might be used as markers for selecting patients that likely to benefit from AI. It would be helpful to include a discuss on a recent in vitro study on PR and aromatase/inflammatory response pathways in breast cancer cells (Hardy DB et al (2008), Mol Endocrinol, 22, p182-1824).

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests