Tamoxifen Metabolism and Breast Cancer Recurrence: A Question Unanswered by CYPTAM

TO THE EDITOR:

In a recent article in *Journal of Clinical Oncology*, Sanchez-Spitman et al[1] report on their prospective clinical study to assess the impact of *CYP2D6* genotype and endoxifen plasma concentrations on relapse-free survival (RFS). They did not observe an association between *CYP2D6* genotype or endoxifen concentrations with RFS in women receiving an admixture of chemotherapy, trastuzumab, tamoxifen, and aromatase inhibitors (AIs), and they concluded that neither *CYP2D6* genotyping nor endoxifen metabolite monitoring are justified for guiding tamoxifen treatment. However, we will articulate several major issues with their study that provide the basis for serious concern regarding their conclusions.

A major consideration when one does a pharmacogenomic study is that the proper population of patients is being studied.[2] In the case of tamoxifen, this population is based on observations demonstrating an association between *CYP2D6* genotype[3,4] and/or endoxifen concentrations[5] with disease-free survival in women receiving tamoxifen monotherapy for the adjuvant treatment of estrogen receptor–positive/human epidermal growth factor receptor 2–negative (ER-positive/HER2-negative) breast cancer. In contrast, *CYP2D6* genotype, which is related to endoxifen concentrations,[6] has not been found to be associated with clinical outcomes in women receiving chemotherapy before treatment with tamoxifen[7] or in women switched to an AI after tamoxifen.[8] A simple explanation is that these additional systemic therapies alter the hazard for both early and late breast cancer events. For example, adjuvant chemotherapy reduces events associated with de novo tamoxifen resistance[9] and endocrine responsive events by suppressing ovarian function in premenopausal women.[10]

Sanchez-Spitman et al[1] performed their power calculations by using data from clinical studies[3,5] of women receiving tamoxifen monotherapy for 5 years for the adjuvant treatment of ER-positive breast cancer. However, instead of enrolling a similar population of women in the CYPTAM study, Sanchez-Spitman et al[1] included women who received prior adjuvant chemotherapy (61%), who were treated with trastuzumab (9%), who were pretreated with tamoxifen (95%), and who then switched to an AI (66%) after a short duration (median, 2.6 years but as short as 3 months) of tamoxifen. Although the underlying assumptions and number of events needed for sufficient power to address the pharmacogenetic and endoxifen concentration questions were specifically lacking in their article, we attempted to perform a power calculation using the hazard ratio of 2.0 in the setting of a similar population of women receiving tamoxifen for 2.5 years.[3] We assumed a 2-year RFS rate of 95% in the poor metabolizers, intermediate metabolizers, and heterozygous extensive metabolizers, an equal number of patients in each group, enrollment period of 3 years, and minimum follow-up of 3 years after close of enrollment. In this situation, a two-sided log-rank test with an overall sample size of 798 patients (399 in each group) achieves 80.0% power at a 0.050 significance level to detect a hazard ratio of 2.02 with an expected number of events of 66. Given that only 255 patients received tamoxifen monotherapy for a short duration, the study by Sanchez-Spitman et al[1] was neither designed nor powered to identify an association between *CYP2D6* genotype or endoxifen concentrations with RFS.

Additional concerns (acknowledged by Sanchez-Spitman et al[1]) are related to their study design that allowed women to enroll up to 12 months after tamoxifen initiation as well as the heavy use of censoring after patients were switched to an AI. Regarding their patient enrollment schema, the design introduced biases because women who recur within the first year of adjuvant tamoxifen treatment do not have the same chance at enrollment as those who recur after the first year of adjuvant tamoxifen treatment. Furthermore, women being considered for the Sanchez-Spitman et al[1] study were enrolled on the basis of their preexisting tolerance to tamoxifen and willingness to adhere to its administration. Other studies were not able to exclude such women because those studies enrolled patients at the time of planned tamoxifen initiation. Regarding the issue of censoring, approximately 66% of the patients were censored after 2 to 3 years of adjuvant tamoxifen (corresponding to approximately 1 to 2 years on study). The statistical methods used to analyze these data assume that censoring is at random and those who are censored have event prospects similar to those who continue on tamoxifen. With such heavily planned censoring for switching treatment, it is unclear what impact this had on the statistical results.

In summary, the following critical question surrounding the pharmacogenomics of tamoxifen remains: What is the impact of *CYP2D6* genotype and/or endoxifen concentrations on the risk for recurrence in women receiving tamoxifen monotherapy for the adjuvant treatment of ER-positive/HER2-negative breast cancer? The

study by Sanchez-Spitman et al[1] was neither designed nor statistically powered to answer this question. Importantly, this question continues to remain globally relevant for hundreds of thousands of women being considered for tamoxifen each year.

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