correspondence

Relevance of Endoxifen Concentrations: Absence of Evidence Is Not Evidence of Absence

TO THE EDITOR:

We read the article by Sanchez-Spitman et al[1] reporting on their CYPTAM study about the association between *CYP2D6* genotype and clinical outcome in the adjuvant treatment of breast cancer with tamoxifen. We acknowledge that a lack of association was shown and that solely the determination of *CYP2D6* genotype has limited relevance for clinical practice in this setting.

However, we do not agree with Sanchez-Spitman et al[1] on their interpretation of the data on the association between endoxifen concentrations (which is the most relevant tamoxifen metabolite) and recurrence of breast cancer. In our opinion, the authors are jumping to conclusions, because the primary end point of this study was not to investigate the relationship between endoxifen concentrations and clinical outcome. Instead, the study was amended in 2017 to explore endoxifen concentrations in relation to recurrence-free survival and was underpowered to draw solid conclusions on this end point, with a hazard ratio of 2.0 as input into their sample size calculations. This hazard ratio cannot be considered realistic to study the effects of endoxifen concentrations on recurrence-free survival.[2]

The CYPTAM study included 662 patients from 2008 to 2011. The trial was originally designed to study *CYP2D6* genotype and recurrence-free survival. According to the protocol, one serum sample was taken for pharmacokinetic purposes (at a random moment during the first year of treatment), and the authors correlated the measured endoxifen concentrations with outcome retrospectively. In 2011, Madlensky et al[3] reported a hazard ratio of 1.4 for patients with endoxifen concentrations below versus above 5.97 ng/mL. Considering this hazard ratio, and the same assumptions as were made in the CYPTAM protocol (2 years of patient inclusion and 2 years of follow-up), a prospectively designed study would have required 276 events in at least 3,150 patients. Importantly, the ratio between patients with endoxifen concentrations below and above the cutoff point (1:4) differs from the ratio between the phenotype groups as assumed in the original sample size calculations in the CYPTAM study (1:1.25). Hence, an even larger sample size would have been required if the correct ratio was taken into account, leading to almost 4,500 patients in the case of 2 years of inclusion and 2 years of follow-up. Sanchez-Spitman et al[1] do not mention the observed number of events, nor do they present a Kaplan-Meier curve for recurrence-free survival stratified for endoxifen concentration that could provide some insight into this number. However, the wide confidence intervals of the hazard ratios for different risks groups suggest a low number of events. In addition, according to the study protocol, several patients with an intermediate or poor metabolizer phenotype received a tamoxifen dose increment temporarily. It is unclear from the article whether these patients were included in this analysis, but if so, this has confounded the outcome of the study. In addition, the authors do not discuss their conflicting results about endoxifen concentrations and clinical outcome in comparison with previous studies.[3-5]

Moreover, just one serum sample does not reflect systemic exposure throughout the tamoxifen treatment course. For example, use of comedication may change over time and may seriously affect systemic endoxifen concentrations.[6] It is known that the combination of tamoxifen and strong CYP2D6 inhibitors is still popular among patients with breast cancer.[7] Therefore, we believe that it is a shortcoming that data on comedication or other factors (temporarily) influencing endoxifen concentrations (eg, low and variable compliance[8]) are missing in this analysis.

Sanchez-Spitman et al[1] conclude their article by stating that "our data do not justify therapeutic drug monitoring based on endoxifen concentrations in patients with breast cancer receiving tamoxifen." However, on the basis of the reflections mentioned previously, this conclusion cannot be drawn from their study, especially in light of the available literature.[3-5] Instead, we are opting for a large prospective—if possible, randomized—clinical trial to study the value of endoxifen-based therapeutic drug monitoring in tamoxifen treatment.[9,10]

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