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TAMOXIFEN ADJUVANT INTERFERERS STUDY (TAIS STUDY): AN EXPLORATIVE ANALYSIS OF (Z)-ENDOXIFEN AND EARLY RECURRENCE OF BREAST CANCER IN A PROSPECTIVE BRAZILIAN STUDY

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Objective: Adherence to treatment and use of co-medication, molecular factors such as CYP2D6 genotype affect tamoxifen metabolism with consequences for early breast cancer (BC) prognosis. CYP2D6 polymorphisms have been promoted as potential biomarkers, yet they only partially explain the variability of plasma (Z)-endoxifen concentrations. The objective of this study was to evaluate whether plasma (Z)-endoxifen levels predicted early BC events (recurrence or death) within 5 years in patients receiving adjuvant tamoxifen treatment. The secondary aim was to evaluate whether (Z)-endoxifen levels were associated with clinical, pathological, and phenotypic CYP2D6 metabolism variables. **Methods:** In a prospective study on 149 tamoxifen-treated early-stage BC patients from Brazil followed up for 5 years, we investigated the association between the active tamoxifen metabolite (Z)-endoxifen at 3 months and event-free survival (EFS) adjusted for clinicopathological factors. We apply this approach to patients from a Brazilian prospective cohort (Tamoxifen Adjuvant Interferers Study) **Results:** In all, 25 (16.8%) patients had recurred or died at a median follow-up of 52.3 months. When we applied a putative 15 nM threshold used in previous independent studies, (Z)-endoxifen levels below the threshold showed an association with shorter EFS in an univariate analysis (p=0.045) and after adjustment for stage (HR 2.52; 95%CI 1.13–5.65; p=0.024). However, modeling of plasma concentrations with splines instead of dichotomization did not verify a significant association with EFS (univariate analysis: p=0.158; adjusted for stage: p=0.117). Hence, in this small exploratory study, the link between impaired tamoxifen metabolism and early BC recurrence could not be unanimously demonstrated. This inconsistency justifies larger modeling studies backed up by mechanistic pharmacodynamic analyses to shed new light on this suspected association and the stipulation of an appropriate predictive (Z)-endoxifen threshold. **Conclusion:** As expected, significant associations with CYP2D6 metabolism phenotypes were detected. In individual and grouped (PM+IM vs. NM+UM) comparisons, PM and IM phenotypes had lower median (Z)-endoxifen levels (7.7 and 16.3 nM, respectively) than patients with NM or UM phenotypes (27.6 and 38.0 nM, respectively; p<0.001). Using a putative clinical threshold concentration of 15 nM, low plasma (Z)-endoxifen levels were associated with a higher rate of early recurrence or death events during follow-up.

Keywords: Tamoxifen. Breast cancer. CYP2D6. (Z)-endoxifen.