Should *CYP2D6* be genotyped when treating with tamoxifen?

“The highly polymorphic *CYP2D6* gene is the principal enzyme of tamoxifen biotransformation to its major active metabolite, endoxifen.”

First draft submitted: 5 October 2016; Accepted for publication: 5 October 2016;
Published online: 24 November 2016

Keywords: *CYP2D6* • drug–drug interaction • pharmacogenetics • tamoxifen

In patients with estrogen receptor positive (ER⁺) breast cancer, the response to tamoxifen can differ among individuals [1]. The highly polymorphic *CYP2D6* gene is the principal enzyme of tamoxifen biotransformation to its major active metabolite, endoxifen [1]. Over the past few years, research has placed great emphasis on the variability of clinical efficacy of tamoxifen, suggesting a correlation between drug metabolism and *CYP2D6* genotype of patients [2]. Many studies aimed at identifying the role of different *CYP2D6* variants found significant association between genotype, phenotype and clinical outcome of patients. Goetz *et al.* showed that patients carrying the *CYP2D6* *4/*4 genotype have a higher risk of disease relapse and a lower incidence of adverse drug reactions, due to the lower metabolic activation of tamoxifen to endoxifen [3]. Schroth *et al.* analysed 206 patients receiving adjuvant tamoxifen monotherapy and 280 patients not receiving tamoxifen therapy (71 months median follow-up), and concluded that genotyping for *CYP2D6* *4, *5, *10 and *41 variants help identify patients who will have little benefit from adjuvant tamoxifen therapy [4]. However, conflicting data are reported on how *CYP2D6* variants could be important determinants of tamoxifen activity and there are few guidelines linking the results of pharmacogenetic tests to specific therapeutic recommendations. Several

clinical trials are reported in literature, with results ranging from a longer disease-free survival interval [5] to a shorter recurrence-free survival time [6] for patients carrying the *CYP2D6* poor metabolizer phenotype. Many factors may have influenced the outcome of studies on *CYP2D6* and its association with tamoxifen efficacy, i.e., tamoxifen combination with inhibitors of *CYP2D6* enzyme and treatment compliance. The ATAC [7] and the BIG 1–98 [8] trials examined the associations between *CYP2D6* genotype and tamoxifen treatment in 1203 and 4392 patients, respectively. None of these studies observed a correlation between *CYP2D6* genotype and clinical outcome with tamoxifen. Nevertheless, many aspects of the ATAC and BIG 1–98 have to be considered: the most important argument is the use of formalin-fixed paraffin-embedded tumor tissues for *CYP2D6* genotyping, instead of germ-line DNA. The use of formalin-fixed paraffin-embedded samples may lead to an important deviation from the Hardy–Weinberg equilibrium (expected vs observed genotype frequencies) for two major reasons: generation of nonspecific products during the polymerase chain reaction [9] and the presence of loss of heterozygosity at the *CYP2D6* locus, resulting in genotyping errors [10]. This issue was confirmed in both the ATAC and BIG 1–98 studies, where the Hardy–Weinberg equilibrium was not respected, with a substantial

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deviation from normal values: $p = 0.000021$ for the ATAC study and $p = 2.5 \times 10^{-92}$ for BIG 1–98 trial [5,7]. Owing to these controversial results, available recommendations do not suggest the use of *CYP2D6* genetic testing to select the best endocrine therapy regimen for patients. In 2006, the US FDA updated tamoxifen label including the information on the increased risk of breast cancer recurrence in poor metabolizer patients, but the subcommittee did not reach a consensus to recommend the *CYP2D6* genotyping [11], and the same conclusion was reached by the National Comprehensive Cancer Network [12]. Additionally, the 2010 guidelines of the American Society of Clinical Oncology [13] and the St. Gallen's expert consensus [14] judged the available data on *CYP2D6* pharmacogenetics insufficient to recommend testing as a tool to determine an adjuvant endocrine strategy. In contrast, on the basis of several studies reporting phenotype and/or genotype data from patients or healthy volunteers [3,15–17] and considering the increased risk for relapse as the main outcome measure, the Dutch Pharmacogenetics Working Group suggested the use of aromatase inhibitors for postmenopausal women with *CYP2D6* poor metabolizer phenotype. Moreover, for intermediate metabolizers, the guidelines suggested the use of aromatase inhibitors or the avoidance of concomitant *CYP2D6* inhibitors, if tamoxifen is the first choice for the specific patient [18]. Indeed, clinicians should be advised that also drug–drug interactions may influence endoxifen plasma concentrations, including co-administration of other drugs, such as selective serotonin reuptake

inhibitors, which interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting *CYP2D6* enzyme [17,19]. Interestingly, the consensus of the National Comprehensive Cancer Network Breast Cancer Risk Reduction Panel is that “...alternative medications that have minimal or no impact on plasma levels of endoxifen should be substituted when possible” even though *CYP2D6* genotyping is not recommended as further validation of this biomarker within the clinical setting is required [20].

To conclude, even though the available recommendations are against the *CYP2D6* screening, the negative results of clinical trials may have been biased by issues in data collection, analysis and interpretation. Hopefully, these recommendations will be revised with the contribution of experts in clinical pharmacogenetics and drug metabolism, in order not to underestimate the negative impact of *CYP2D6* inhibitors that may be administered during tamoxifen therapy and potentially decrease the concentrations of the active metabolite endoxifen.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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