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Short communication

Therapeutic Drug Monitoring of endoxifen as an alternative for *CYP2D6* genotyping in individualizing tamoxifen therapy

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ABSTRACT

Different strategies have been proposed to individualize tamoxifen treatment in order to improve recurrence-free survival in estrogen receptor (ER)-positive breast cancer. To date, the debate remains on which strategy should be used. The objective of this viewpoint is to highlight Therapeutic Drug Monitoring of endoxifen, the active tamoxifen metabolite, as the preferred methodology compared to *CYP2D6* genotyping for individualizing tamoxifen therapy for ER-positive breast cancer patients treated in the adjuvant setting.

1. Introduction

Individualization of tamoxifen treatment to improve recurrence-free survival in estrogen receptor (ER)-positive breast cancer patients has been investigated for years. The use of genotyping of metabolizing enzymes (mainly *CYP2D6*) to predict exposure to endoxifen, the most important active metabolite of tamoxifen, has widely been advocated. The underlying assumption of genotyping is, that it predicts endoxifen concentrations and that the exposure to endoxifen is related to breast cancer treatment outcome. However, the individual genotype is just one of many factors that explains variability in endoxifen exposure. Therefore, we propose to measure endoxifen concentrations for therapy individualization instead of genotyping.

2. *CYP2D6* genotyping

The association between the *CYP2D6* genotype and breast cancer outcome has extensively been researched resulting in conflicting results. In order to find a conclusive answer, results of multiple studies have been analyzed in a meta-analysis [1], which demonstrated no association between *CYP2D6* genotype and breast cancer outcome. However, a further analysis of this meta-analysis demonstrated that the *CYP2D6* genotype is associated with disease-free survival in a subset of patients who received tamoxifen as adjuvant therapy at a dose of 20 mg/day for 5 years. This analysis, in turn, has been criticized because it excluded the ABCSG8, ATAC and BIG1-98 trials, three large prospective clinical studies, and lacked *a-priori* specified criteria for the sub analysis [2]. Thus, to date, no conclusive answer on the predictive value of the *CYP2D6* genotype in tamoxifen treatment for breast cancer outcome exists. Nevertheless, genotyping has been proposed as a strategy to individualize tamoxifen therapy. Recently, a guideline by the Clinical Pharmacogenetics Implementation Consortium (CPIC) has been published that provides therapeutic recommendations based on the *CYP2D6* genotype for ER-positive breast cancer patients who are indicated to receive adjuvant tamoxifen for 5 years [3]. In this guideline, the *CYP2D6* genotype is classified into five different metabolizer phenotypes with activity scores (AS; in brackets) namely CYP2D6-ultrarapid (>2.0), -normal (1.5 and 2.0), -normal or intermediate (1.0), -intermediate (0.5) and -poor metabolizers (0). The AS are supposed to reflect systemic exposure to endoxifen and with that the expected clinical endpoints of recurrence and event-

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free survival. Patients with an AS >1.5 are expected to reach therapeutic endoxifen concentrations and start with 20 mg tamoxifen daily. Alternative hormonal therapy is advised for all patients with an AS of 1.0 or lower. Tamoxifen dose should only be increased to 40 mg if AS is 1.0 or lower and if aromatase inhibitor use is contraindicated, according to the drafters of the guideline [3].

3. Therapeutic Drug Monitoring of endoxifen concentrations

The predictive value of endoxifen plasma concentrations has been substantiated by a large retrospective analysis. An endoxifen threshold concentration of 5.97 ng/mL was identified and demonstrated that patients above this target had a 26% lower risk of getting recurrent disease [4]. A similar threshold has been identified by Saladores et al. [5]. Contrary to these aforementioned findings, a recent prospective study showed no significant relation between endoxifen concentrations and objective response rate, progression free survival or clinical benefit [6]. Of note, the patients in this trial were treated in a neo-adjuvant- and metastatic setting and can therefore not be compared to adjuvantly treated patient cohorts. In addition, a threshold of endoxifen concentrations was not evaluated.

Based on the findings of Madlensky et al. [4], Therapeutic Drug Monitoring (TDM) of endoxifen has been implemented in certain hospitals to improve treatment outcomes. Patients treated in our hospitals indicated to receive tamoxifen in the adjuvant setting initiate treatment with 20 mg tamoxifen daily. After every three months, when endoxifen concentrations are at steady state, a blood sample is drawn and analyzed. Patients continue with 20 mg tamoxifen daily when the endoxifen concentration is above 6 ng/mL. If the concentration is below 6 ng/mL, a dose increment to 40 mg tamoxifen daily is prescribed and re-evaluated after three months. In case this threshold level of endoxifen is not reached with the proposed dose increment, physicians consider a switch to alternative hormonal therapy, like aromatase inhibitors. Aromatase inhibition in postmenopausal women with ER-positive early breast cancer has demonstrated to be superior to tamoxifen treatment. Besides, the combination of aromatase inhibition and ovarian suppression (pharmacologically or by ablation) has shown to improve disease-free survival compared to tamoxifen treatment in premenopausal women [7,8]. Therefore, a proposed switch to these therapies in case of sub therapeutic endoxifen concentrations has clinical validation. However, ovarian suppression can cause substantial side effects and the combination of an aromatase inhibitor and ovarian ablation did not show a difference in overall survival compared to tamoxifen for premenopausal women [8]. Additionally, it is well known that some patients tolerate tamoxifen better than aromatase inhibitors and vice versa. As a consequence, not all patients are able to switch to aromatase inhibitors, making correct identification of patients at risk even more pivotal.

The question now can be raised whether it may be better to measure endoxifen levels rather than performing *CYP2D6* genotyping in patients treated with adjuvant tamoxifen.

4. Advantages of Therapeutic Drug Monitoring of endoxifen

As previously described, studies that have linked *CYP2D6* genotype with clinical outcome yielded conflicting results and have been heavily criticized [2]. Not all CYP2D6 poor and intermediate metabolizers have defined sub optimal levels of endoxifen and not all extensive or ultra-rapid metabolizers reach therapeutic concentrations of endoxifen [4,9]. In other words, *CYP2D6* genotyping does not fully explain variability in endoxifen concentrations: only 34–52% of the variability in endoxifen concentrations is explained by the *CYP2D6* genotype [10]. The residual, unexplained variability is thus high and may be attributed to a long list of other non-*CYP2D6* genotype dependent factors including co-medication, organ function, life style, other genetic factors (*e.g.* drug transporters), patient characteristics (age, gender, body size), adherence and those factors that are still unknown and may all vary over time. Periodic measurement of endoxifen concentrations has many advantages and can be regarded as a better defined outcome measure of all these effects than the static *CYP2D6* genotype alone. TDM will identify patients with low endoxifen levels that otherwise go unnoticed by genotyping, *e.g.* non-adherence and unrecognized concomitant use of CYP2D6 inhibitors. The latter, undetected by genotyping, may even turn an ultra rapid metabolizer into a poor metabolizer with all clinical consequences which may also be the case for patients carrying rare genomic variants, that are not included in the genotype test. Other limitations of genetic testing are the inadequacy to detect *de novo* variants and that uncertainty exists on which single nucleotide polymorphisms need to be evaluated. In addition, the translation from genotype to phenotype has not been standardized. Measurement of endoxifen concentrations overcomes these challenges.

Feasibility of TDM of endoxifen has been demonstrated by the TADE study, where a dose increment was applied in patients with sub optimal concentrations of endoxifen, leading to therapeutic concentrations in most patients [11]. TDM can also evaluate the effect of tamoxifen dose increments on the endoxifen concentration. It has been demonstrated that endoxifen serves as *a proxy* for the anti-estrogen effect of tamoxifen and metabolites [12], therefore only the endoxifen concentration is required for TDM.

It can be argued that dose adjustments based on TDM of endoxifen can only be applied after approximately three months of treatment, when endoxifen concentrations are at steady state. However, this short timeframe of potential sub optimal dosing is not expected to be clinically relevant, since tamoxifen treatment is indicated to reduce recurrence and mortality rates after years of treatment. Another obstacle for implementation faced by TDM of endoxifen is lack of bioanalytical method selectivity, which can result in misinterpreting plasma concentrations. However, an established selective bioanalytical method for the quantification of endoxifen is easy to implement and available [13].

5. Conclusion and perspective

In conclusion, we believe, that TDM of endoxifen allows for better identification of patients with low endoxifen concentrations compared to the *CYP2D6* genotype or related activity score. Eventually, patients could start on an individualized dose based on genotyping results until steady state is reached and TDM can be performed. Subsequently, patients with an indication for adjuvant treatment with 20 mg tamoxifen daily for 5 years but low endoxifen concentrations should get a dose increment to 40 mg daily. If sub therapeutic concentrations remain, patients can switch to treatment with aromatase inhibition or aromatase inhibition with ovarian suppression.

We do recognize that both TDM of endoxifen and *CYP2D6* genotyping, lack prospective validation and that the irrefutable proof for a target level has not been provided for adjuvant tamoxifen ER+ breast cancer treatment. Randomized, prospective TDM trials should fill this gap and provide proof for therapy adjustments based on endoxifen concentration and/or *CYP2D6* genotypes. Such studies, however, require an extremely large sample size and a lengthy follow up. Therefore, prospective validation is not likely to be established on short-term. Even if such a study would be initiated now, debates about tamoxifen therapy improvement remain important, since the question remains: how do we treat our patients best in the meantime?

Conflicts of interest

The authors declared no competing interests for this work. No funding was received for this work.

Ethical approval

Approval by an ethics committee was not required for this manuscript.

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