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Überörtliche Berufsausübungsgemeinschaft
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Laboratory information 6/2017

Genetics in ER+ breast cancer therapy using Tamoxifen

Medical background

Tamoxifen has been used for several years in adjuvant therapy in the treatment of estrogen receptor-positive (ER+) breast cancer. The prodrug tamoxifen, which is only inadequately effective, is metabolized by cytochrome P450 2D6 (gene: CYP2D6) into the potent metabolites 4-OH-tamoxifen and 4-OH-N-desmethyl-tamoxifen (endoxifen). This produces endoxifen in a 100-fold higher concentration than 4-OH-tamoxifen. The endoxifen formation is therefore decisive for the efficacy of tamoxifen.

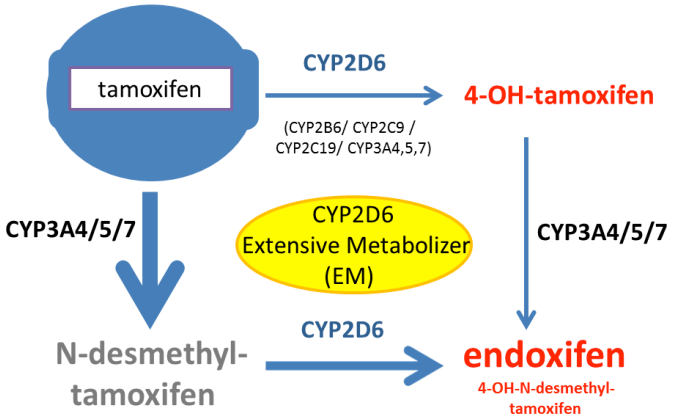

Figure: Tamoxifen metabolism. Extensive metabolizer indicates a normal CYP2D6 activity.

However, the sequence of the CYP2D6 gene is highly variable in the populations, influencing the enzymatic activity of cytochrome P450 2D6. Some genotypes are associated with a loss of enzyme activity (Poor Metabolizer, PM) whereas others are associated with increased enzyme activity (Ultrarapid Metabolizer, UM). In addition, the enzyme activity can also be blocked by some drugs (e.g.: selective serotonin reuptake inhibitors (SSRI)).

Method for analysis

For several years in breast cancer patients under tamoxifen therapy CYP2D6 was genotyped retrospectively in smaller studies. Genotypes associated with reduced or missing enzyme activity showed a significantly higher recurrence risk and poorer therapy outcome. In 2009, a larger retrospective study with 1325 patients appeared, confirming the association between success of tamoxifen therapy and CYP2D6 genotype. Prospective investigations have yet to be finished. Nonetheless, breast cancer centers and medical specialists have already reacted to the new data situation. As an alternative to tamoxifen delivery, aromatase inhibitors (AI) can be treated, but this can lead to increased side effects and can only be used postmenopausal.

Analytics

In the past 8 years, more than 1200 samples have been analyzed in our laboratory, taking into account 28 polymorphisms, duplications and deletions of the CYP2D6 gene. Only about 38% of the patients had a genotype, which is associated with an optimal tamoxifen effect (if no inhibitory co-medication (e.g. SSRI) exists). For approximately 50% of the cases, the genotype predicted a suboptimal efficacy of tamoxifen. In the genotypes which had only one allele with reduced enzyme activity (IM allele, approx. 12%), the conclusion remained blurred. In order to confirm the analytical significance of CYP2D6 genotyping, we also offer drug monitoring of tamoxifen and its most important metabolites for patients with tamoxifen therapy in addition to molecular-genetic diagnostics.

Indications for CYP2D6 genotyping

Before and during therapy of estrogen receptor positive breast cancer with tamoxifen.

Methods

Genotyping: PCR, sequencing for the detection of at least 28 polymorphisms of CYP2D6 at the same time. Duplication (XN allele) and deletion (* 5 allele) analysis are performed by Multiplex Ligation Probe Amplification (MLPA) detection.

Pharmacology: Tamoxifen as well as its metabolites (N-Desmethyl-Tamoxifen, 4-OH-Tamoxifen and Endoxifen) can be quantified by HPLC.

Material and pre-analysis

Genotyping: 2 ml EDTA blood
Pharmacology: Cooled, light-protected 2 ml of EDTA blood + whole blood in serum tubes. Please contact us for further information.
On our homepage www.labmed.de/en you will find a form for clinical data, together with a declaration of consent. Please fill in and send together with the sample material.

Turnaround time and reporting

Genotyping: TAT approx. 10-14 days.
For each medical report, we supply an individual interpretation along with further diagnostic recommendation.

Contact

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Literature

1. Schroth et al., Association Between CYP2D6 Polymorphisms and Outcomes Among Women With Early Stage Breast Cancer Treated With Tamoxifen, 2009, JAMA. 2009 Oct 7; 302(13): 1429–1436.
2. Del Re et al., Should CYP2D6 genotyped when treating with tamoxifen, Pharmacogenomics 2016, 17:1967-1969.