Enriching medication review with a pharmacogenetic profile
a case of tamoxifen adverse drug reactions

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Introduction

Pharmacogenotyping is applied to determine the hereditable component of a patient's susceptibility to experience therapy failure and/or adverse drug reactions (ADRs). We present the case of a female patient diagnosed with breast cancer and treated with tamoxifen as recurrence therapy who experienced various ADRs.

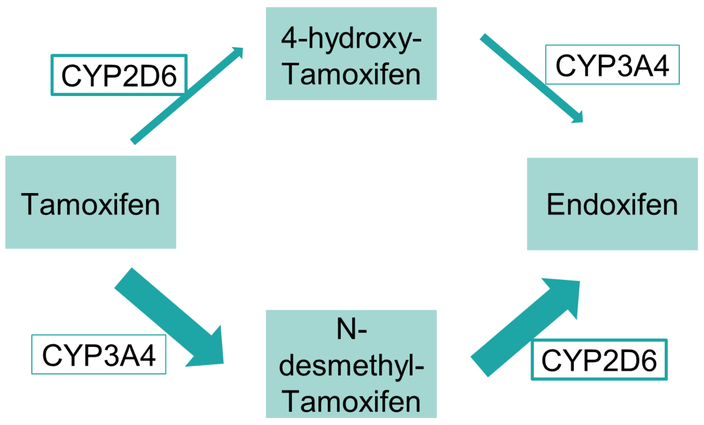

Figure 1: The major metabolite of tamoxifen is formed by demethylation catalyzed by CYP3A4 among other CYPs. The metabolite N-desmethyl-tamoxifen is then oxidized by CYP2D6 to endoxifen, which is up to 100 fold more active than tamoxifen.
(adapted after Klein et al. PharmGKB, 2013)

Methods

After an initial medication review by a pharmacist, pharmacogenetic panel testing was conducted applying the commercial test Stratipharm® by humatrix AG (Pfungstadt, Germany). The Stratipharm® tool provides not only the results of genetic testing, but also drug-specific interpretation of the corresponding phenotype (pharmacogenetic profile) according to available evidence, see Figure 2 for warning levels.

Figure 2: Warning levels by Stratipharm®: normal; indication; suspicion; danger

Results

We gathered the patient's medication (see Table 1), analyzed the pharmacogenetic profile revealing variants in three cytochrome P450 (CYP) enzymes (see Table 2), and gave recommendations (see Figure 3).

Table 1: Patient's medication at the time of the medication review

Substance	Dosage	Indication
Tamoxifen 10 mg	0-0-1	Adjuvant endocrine therapy of breast cancer after mastectomy
Mistletoe preparation	as needed	Supportive herbal cancer therapy
Ibuprofen 600 mg	as needed: 0.5-0.5-0.5	Pain after car accident
Metamizole 500 mg	as needed	Pain after car accident
Pantoprazole 20 mg	1-0-0	As long as therapy with ibuprofen
Lorazepam 1 mg	as needed	Difficulties falling asleep

Table 2: Pharmacogenetic profile of the patient

Gene	CYP2D6	CYP2C19	CYP2C9
Annotation, Genotype	rs5030655, T/-; rs28371725, G/A	rs12248560, C/T	rs1799853, C/T
Haplotypes	*6/*41	*1/*17	*1/*2
Predicted Phenotype	Intermediate Metabolizer	Ultrarapid Metabolizer	Intermediate Metabolizer

Tamoxifen: CYP2D6 Intermediate Metabolizer

→**PGx result**: Suspicion of **ineffectiveness**: decreased enzyme activity in CYP2D6 leads to insufficient activation of the prodrug tamoxifen to the major active metabolite endoxifen. In this patient, only part of the tamoxifen is activated to the active metabolite endoxifen.

→**Recommendation** : *Stop tamoxifen and switch to a monthly injection of **leuprorelin 3.75 mg** as ovarian suppression (due to the premenopausal status of the patient) and supplement with **letrozole 2.5 mg** once daily initiated two weeks after the initiation of leuprorelin.*

Note: Stratipharm® did not report results related to any other genes relevant for tamoxifen metabolism.

Ibuprofen: CYP2C9 Intermediate Metabolizer

→**PGx result**: Indication for **intolerance**: decreased enzyme activity in CYP2C9 leads to higher risk for adverse drug reactions, e.g., gastrointestinal bleedings.

→ **Recommendation** : *Ibuprofen should be used only **short-term** and at **the lowest effective dose** for pain.*

Pantoprazole: CYP2C19 Ultrarapid Metabolizer

→ **PGx result**: Suspicion of **ineffectiveness**: increased enzyme activity in CYP2C19 leads to higher degradation of pantoprazole.

→**Recommendation: *Rabeprazol** should be used as proton pump inhibitor (as there is no major metabolism via CYP2C19 expected).*

Figure 3: Drug boxes with PGx result (result of pharmacogenotyping); **Note**: There are no pharmacogenetic data for mistletoe preparation, metamizole and lorazepam.

Conclusion

As a result of this pharmacist-led medication review supplemented with pharmacogenetic panel testing, concrete genotype-driven recommendations for the treating gynecologist were compiled. Contrary to our expectations (due to the patients' experienced ADRs), the pharmacogenetic profile revealed that tamoxifen was propably not sufficiently activated in the patient, thereby resulting in ineffectiveness. This case revealed the added value of a large pharmacogenetic panel test and the complexity of integrating a pharmacogenetic profile into a recommendation.

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