THE ROLE OF CYP2D6 POLYMORPHISMS IN BREAST CANCER PATIENTS

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DESCRIPTION

• Breast cancer is the 2nd cause of death and the 1st diagnosed neoplasia among women in developed countries. Its incidence is increasing, whereas mortality is decreasing.
• Breast cancer diversity urges the application of personalized medicine.

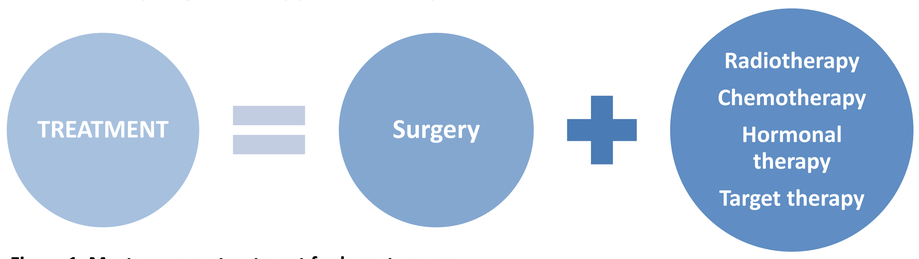

Figure 1. Most common treatment for breast cancer.

• Treatment choice depends on risk of recurrence, clinical stage and predictive factors.
• Drugs present a wide range of pharmacokinetics, pharmacodynamics, toxicity and tolerance in individuals that may be explained by the presence of **GENETIC POLYMORPHISIMS.**

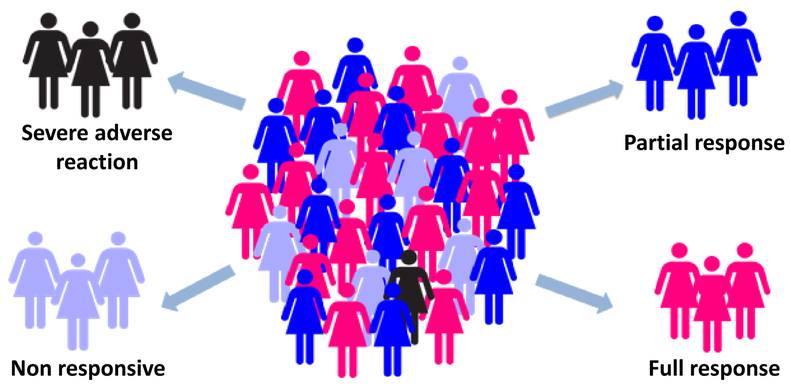

Figure 2. Degrees of tolerance to breast cancer drugs.

OBJECTIVE

The aim of this review is to describe the pharmacogenetics and response of breast cancer patients to tamoxifen, the role that CYP2D6 has on it and whether it can be used as a reliable biomarker.

TAMOXIFEN

Tamoxifen is an efficient treatment for early stages of breast cancer, with low risk of recurrence. It blocks the action of the estrogen, therefore suitable for tumors with specific estrogen receptors. (1)

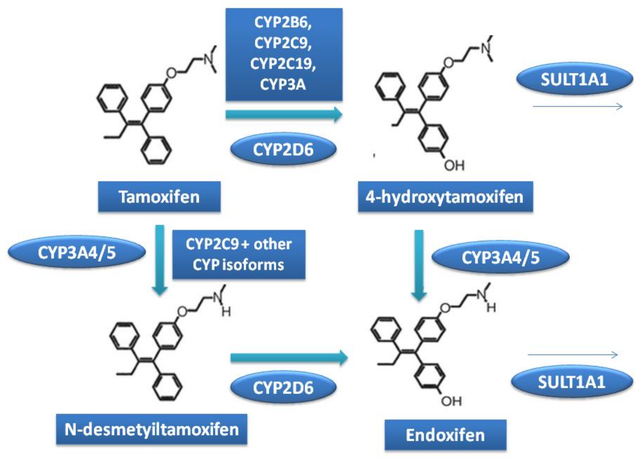

Figure 3 . Tamoxifen metabolism. (1)

GENES related to Tamoxifen **EFFICACY**:

- •CYP3A4
- •SULTIAI
- •CYP2C19
- •CYP3A4/5
- •CYP2B6
- •CYP2C9
- •CYP2D6
- •Among others

Tamoxifen activity is mediated by cytochrome P450 2D6 (**CYP2D6**) (2)

Genetic polymorphisms may affect tamoxifen concentrations, its metabolites and the effectiveness of the drug.

CYTOCHROME P450 2D6 (CYP2D6)

• CYP2D6 is a cytochrome P450 expressed in the liver, whose lack of activity leads to the formation of inactive truncated proteins.

88 allelic variants of CYP2D6 have been described, which can be classified in four different **PHENOTYPIC GROUPS** (2)

Type of metabolizer	CYP2D6 Genetic variants
Ultraextensive metabolizer (UM)	CYP2D6 *1xN
	CYP2D6 *2xN
	CYP2D6 *35xN
	CYP2D6 *41xN
Extensive metabolizer (EM), (wt alleles)	CYP2D6 *1
	CYP2D6 *2
	CYP2D6 *35
Intermediate metabolizer (IM)	CYP2D6 *9
	CYP2D6 *10
	CYP2D6 *17
	CYP2D6 *41
Poor metabolizer (P), (Null alleles)	CYP2D6 *3
	CYP2D6 *4
	CYP2D6 *5
	CYP2D6 *6
	CYP2D6 *7
	CYP2D6 *8
	CYP2D6 *11
	Rare variants: *12, *13, *14, *15, *16, *18, *19, *20, *21, *38, *40, *42, *44, *56, *62

Table 1. CYP2D6 most common genetic variants classified in phenotypic groups.

	Poor metabolizer (PM)	Intermediate metabolizer (IM)	Extensive metabolizer (EM)	Ultraextensive metabolizer (UM)
CYP2D6 (Asians)	0% - 8.9%	5 - 25%	70% - 90%	0% - 0.9% (Saudi Arabian 21%)
CYP2D6 (Caucasians)	3.2% - 12.6%	1% - 2%	71% - 85%	0.8% - 10%
CYP2D6 (Africans)	0% - 19%	18% - 37%	55% - 79%	4.9% (Ethiopians 29%)
CYP2D6 (Hispanics)	0% - 5.9%	<1%	~90%	0% - 1.7%
Metabolism status	Slow	Reduced	Normal	Very fast

Table 2. Polymorphisms frequencies among phenotypic groups.

DISTRIBUTION of the individuals can be different according the ethnicity they belong to

- **Worst outcomes after tamoxifen treatment**: CYP2D6 alleles *4, *5, *10, and *41. (3)
- **Recurrence rates**: EM 14.9%, E/I M 20.9%, and PM 29.0%. (4)
- **Mortality rates:** 16.7% for EM, 18.0% for E/I M, and 22.8% for PM. (4)
- There is an association between PM CYP2D6 alleles and the worst outcomes of disease-free survival. (4)

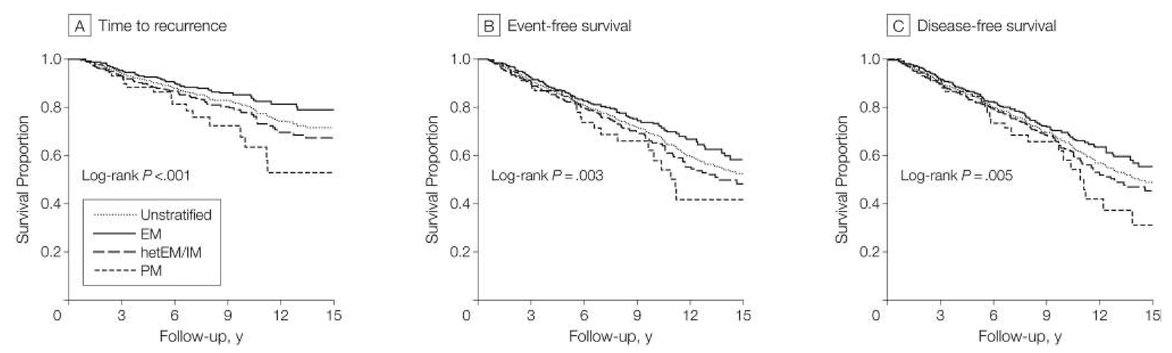

Figure 4. Kaplan-Meier of: time to recurrence, event-free survival and disease-free survival for CYP2D6 EM, EM/IM and PM phenotypes (4)

OTHER INVOLVED ENZYMES

- CYP2C19 *17 → better outcomes. (3)
- SULT1A2*2 and SULT1A2*3 → higher 4-hydroxy-tamoxifen and endoxifen plasma levels. (5)

- CYP3A5 *3/*3 treated with tamoxifen during 2 years → higher risk of recurrence. (6)
- CYP3A5 *3/*3 treated with tamoxifen during 5 years → increased disease-free survival rate. (6)

STATE OF THE ART

• The Roche DNA microarray-based pharmacogenetics test for CYP2D6 and CYP2C19 variants (approved by FDA), called **AmplyChip CYP450** test, allows the identification of 27 of the different CYP2D6 variants. But it is not recommended applying the CYP2D6 test yet. (7)
• The **Hap Map Project**, has the aim to determine the haplotype of four different population groups, in order to identify the candidate genes with the correct haplotype labeling SNPs. (4)

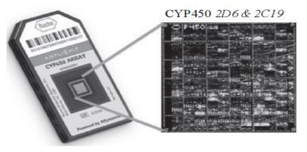

Figure 5. AmplyChip CYP450 (7)

CONCLUSIONS

• There is an association between CYP2D6 genetic variants and tamoxifen outcomes in breast cancer patients, having CYP2D6 a gene-dose effect.
• Best outcomes correspond to ultraextensive and extensive metabolizers, while the worst to intermediate and poor metabolizers.
• Tamoxifen metabolism may involve different genes, pathways, and combinations of them.

More trials are needed before CYP2D6 can be used as a reliable biomarker of tamoxifen effectiveness in breast cancer patients.

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