Impact of tamoxifen dose on tamoxifen and its active metabolites levels in breast cancer patients: preliminary results from a prospective, open-label trial

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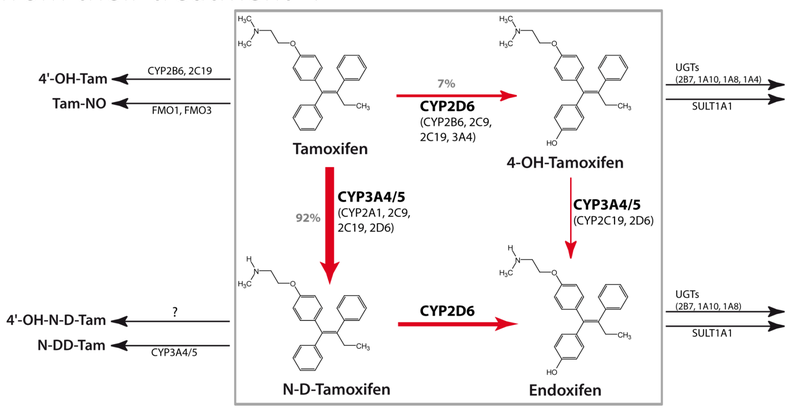
Background

Tamoxifen is still a widely used drug for the adjuvant treatment of endocrine-sensitive breast cancer.

Tamoxifen is considered as a pro-drug that is metabolized into pharmacologically active metabolites, mainly endoxifen.

CYP2D6 is a key enzyme responsible for tamoxifen bioactivation into endoxifen.

CYP2D6 gene is highly polymorphic and patients with null (PM) or reduced (IM) CYP2D6 activity display lower endoxifen concentrations and thus could achieve less benefit from their treatment [1].



Objective

- **To assess the influence of doubling *Tamoxifen* dose (to 20 mg twice daily) on endoxifen levels in the different CYP2D6 genotype groups classified as: poor-, intermediate-, extensive- and ultra-rapid metabolizers (respectively PM, IM, EM and UM).**

The reported data are preliminary results from an ongoing larger prospective, open-label trial studying tamoxifen metabolism in breast cancer patients and the impact of tamoxifen dose on the level of the active metabolites (NCT00963209).

Methods

Inclusion:	CYP2D6 genotyping Tamoxifen & metabolites levels
Day 0 (d0):	CYP2D6 and CYP3A4 phenotyping Tamoxifen & metabolites levels
Day 30 (d30): **Day 90 (d90):** **Day 120 (d120):**	Tamoxifen & metabolites levels

Tamoxifen and Metabolites levels measurements in plasma

Performed with an ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method [2].

CYP2D6 genotyping analyses

For most frequent null alleles (*3, *4, *5, *6) and for gene duplication /multiplication (*XN).

CYP2D6 phenotyping test

Dextromethorphan metabolic ratio (DM/DX) test was used for the determination of CYP2D6 activity [3,4].

CYP3A4/5 phenotyping test

Midazolam metabolic ratio test was used for the determination of CYP3A4 activity [5].

Eligibility criteria

- ✓ Patients treated with tamoxifen for ≥ 4 months.
- ✓ No history of deep venous thrombosis or pulmonary embolism.
- ✓ No history of endometrial carcinoma.
- ✓ No history of vaginal bleeding, endometriosis, endometrial, hyperplasia, endometrial hypertrophy and/or polyps.
- ✓ No pregnant or lactating women.
- ✓ No known allergy to midazolam or dextromethorphan.

Treatment adherence assessment

Each patient completed an anonymized questionnaire to report semi-quantitatively her treatment adherence.

Statistical considerations

CYP2D6 genotypes were categorized into four groups and scored on the basis of the number of *CYP2D6* functional alleles. A score of 0 was given to PM, 1 for IM, 2 for EM and 3 for UM (multiple functional alleles). Heterozygous genotypes with a null functional allele/multiple functional allele (*4/*XN) have been scored according to the DM/DX test predicted phenotype.

Tamoxifen and metabolites trough plasma levels, measured 6 to 24 hours after last drug intake, were log-transformed to normalize their distribution. ANOVA was used to evaluate endoxifen levels increase and difference between the CYP2D6 genotypes before and after doubling *Tamoxifen* dose. All data analyses were conducted with Stata statistical software (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP).

Results

76 patients were available for analysis, with trough plasma levels (6 to 24 hours post-dose).

11 patients were treated with potentially interacting co-medications (CYP2D6 inhibitors) : 3 citalopram, 2 escitalopram, 5 venlafaxine, 1 paroxetine.

Patient characteristics		
Median Age (range)		51 years (33 – 79)
Ethnic groups	Caucasian North African Indian	73 2 1
Premenopausal Postmenopausal		38 38
Tumor histology	Ductal invasive Lobular invasive Other invasive subtypes Ductal in situ	49 15 7 5
Reported adherence		> 80 %
		Number of patients
CYP2D6 genotype activity score	0 (PM) ● 1 (IM) ■ 2(EM) ▲ 3 (UM) ◆	3 23 47 3

Tamoxifen and metabolites levels reached steady state 30 days under *Tamoxifen* 20 mg bid :

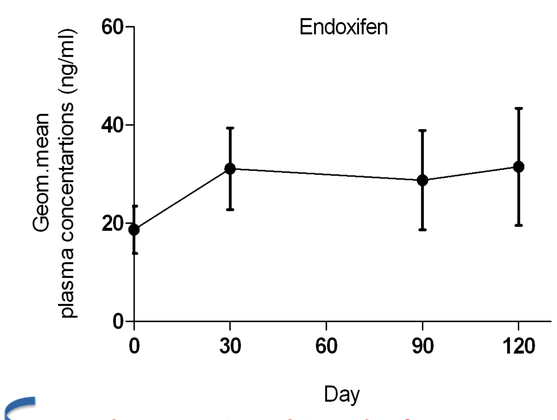
data from 42 patients (over 76 patients) with tamoxifen and metabolites levels available at least for d0, d30 and d90.

	Geometric mean (ng/ml)	CV (%)	fold increase (CV%), *P* value
Tamoxifen ***20** mg* (d0)	134	48	1.8 (22), <0.0001
Tamoxifen ***40** mg* (d30)	246	46	
N-D-Tam ***20** mg* (d0)	246	53	1.7 (23), <0.0001
N-D-Tam ***40** mg* (d30)	413	48	
4-OH-Tam ***20** mg* (d0)	2.3	44	1.6 (22), < 0.0001
4-OH-Tam ***40** mg* (d30)	3.7	51	
Endoxifen ***20** mg* (d0)	18.7	89	1.7 (25), 0.005
Endoxifen ***40** mg* (d30)	31.1	92	

Comparison between steady state endoxifen concentrations under 20 mg qd and 20 mg bid *Tamoxifen* dose as function of genotype based CYP2D6 activity score.

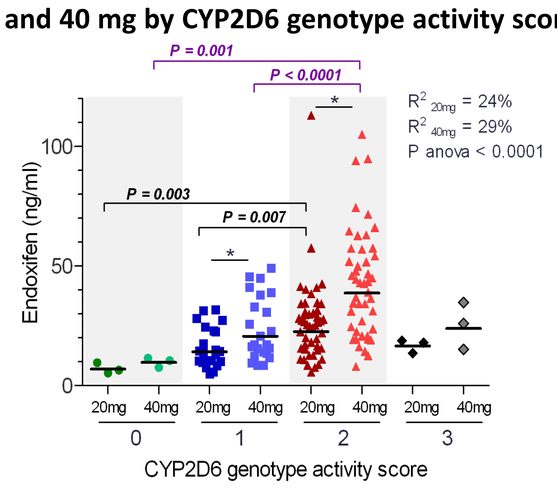
	Geometric mean (ng/ml), CV%				fold increase (CV%)				P_{anova}, R^2 (%)
CYP2D6 genotype activity score	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	
Endoxifen (Css_{20mg})	6.9 (36)	14.2 (69)	22.6 (76)	16.6 (19)	1.4 (28)	1.5 (29)	1.7 (29)	1.4 (59)	0.07, 9%
Endoxifen (Css_{40mg})	9.7 (24)	20.7 (76)	38.7 (85)	23.9 (52)					
P value	0.7	<0.0001	<0.0001	0.2					

Figure 1: Endoxifen accumulation under *Tamoxifen* 40 mg (n = 42) ; (Geom. mean, 95%CI)



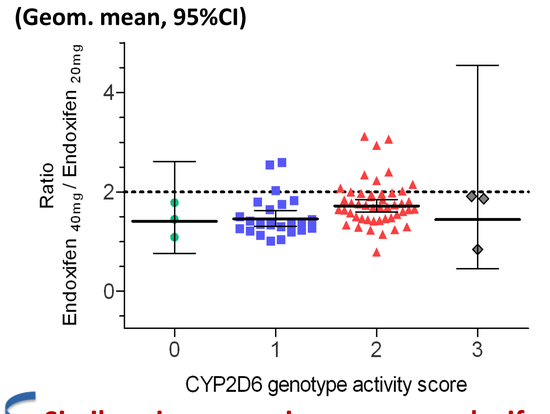
Steady state is achieved after 30 days of treatment.

Figure 2: Steady state Endoxifen levels under *Tamoxifen* 20 mg and 40 mg by CYP2D6 genotype activity score (n = 76).



Endoxifen levels are different between EM and PM, and EM and IM at both regimen and show an important inter-individual variability.

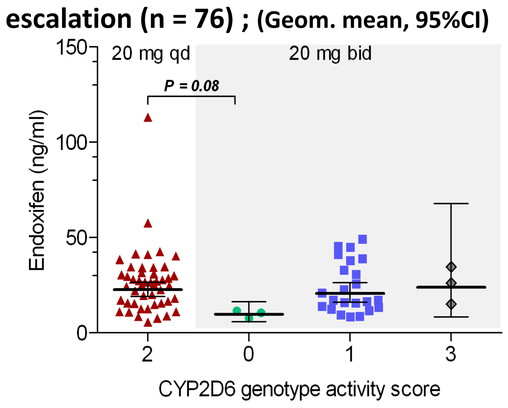
Figure 3: Extent of endoxifen levels increase per CYP2D6 genotype activity score (n = 76) ; (Geom. mean, 95%CI)



Similar increase in mean endoxifen levels between CYP2D6 groups.

Endoxifen level increased less than a two-fold.

Figure 4: Comparison between endoxifen levels in EMs at baseline and in IMs, PMs and UMs after *Tamoxifen* dose escalation (n = 76) ; (Geom. mean, 95%CI)



Doubling Tam dose seems to compensate for previously observed differences in mean baseline endoxifen levels between EM and IM under the standard (20mg) *Tamoxifen* dose ; in PM the compensation might be insufficient yet.

Conclusions

- ✓ **Endoxifen concentrations vary widely between and within each CYP2D6 phenotype groups.**
- ✓ **Genotype based CYP2D6 activity score explains only a minor part of this variability (< 30%).**
- ✓ **Increase in *Tamoxifen* dosage increases mean endoxifen levels less than 2 fold, and to a similar extent across CYP2D6 phenotype groups; it seems sufficient to compensate for the reduced CYP2D6 activity in IM.**
- ✓ **Direct endoxifen monitoring might represent a better approach to evaluate actual endoxifen exposure in an individual, and to adjust dosage regimen consequently.**
- ✓ **A population pharmacokinetic analysis of tamoxifen, endoxifen and other major tamoxifen metabolites will be performed in order to characterize their kinetic profile and to quantify the influence of genetic and non-genetic factors on drug and metabolites levels, which would be useful for *Tamoxifen* dose optimization strategies.**

References

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