TAMOXIFEN METABOLISM AND THE IMPACT OF TAMOXIFEN DOSE ON THE LEVEL OF THE ACTIVE METABOLITES IN ENDOCRINE SENSITIVE BREAST CANCER PATIENTS

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Background

Breast cancer (BC) is the most common cancer in women[1,2]. 60-70% of newly diagnosed BC have tumours that express estrogen receptor and/or progesterone receptor (ER/PR). These patients will be recommended and benefit from endocrine therapy[3] .

Tamoxifen is the most widely used hormonal therapy for the treatment and prevention of hormone-dependent beast cancer[4]. It is considered to be a "prodrug" that requires conversion, by cytochrome P450 (CYP) enzymes into its pharmacologically active metabolites, notably endoxifen (Figure 1).

The clinical response to tamoxifen varies widely among patients and not all women with hormone positive breast cancer benefit from tamoxifen. The identification of the determinants of this variability is important, to predict the benefits of tamoxifen to an individual and to rational optimization of endocrine therapy[5].

CYP2D6 genotypes have been shown to determine the level of endoxifen and to predict outcome in patients treated with tamoxifen. This prompted to consider a potential role for CYP2D6 genotyping in therapeutic decisions. However, a large inter-patient variability in endoxifen levels still subsist even after correcting for CYP2D6 status[6,7,8].

Endoxifen levels could represent a better surrogate marker of tamoxifen efficacy, as its level depends also on the activity of other cytochromes (CYP3A4/5, 2C9, 2C19) and drug interacting comedications, as CYP2D6 inhibitors, frequently prescribed to treat tamoxifen-induced hot flashes.

Several studies provided correlation between CYP2D6 genotype/phenotype and tamoxifen metabolism as well as between CYP2D6 genotype and clinical outcomes[7,8]. However, the relationship between endoxifen levels and clinical outcomes has not been evaluated, and the value of monitoring endoxifen plasma concentrations has yet to be explored.

Primary Objectives

Determine how the increase of tamoxifen dose influences the level of its major metabolites in the different genotype groups (poor-, intermediate-, and extensive-metabolizers) in patients with hormone-sensitive breast cancer.

Secondary Objectives

- Characterize the population pharmacokinetic profile of tamoxifen and its metabolites, together with inter- and intra-patient variability, and quantify the influence of genetic and non-genetic factors on drug levels.
- Investigate the role of the other CYPs (CYP3A4, CYP2C19), conjugation enzymes, and drug transporters in the pharmacokinetics of tamoxifen, and the impact of their polymorphism on drug and metabolites levels.
- Confirm a relation between hot flashes and CYP2D6 genotypes and/or active metabolites levels, and evaluate the role of this clinical symptom assessment in the monitoring of tamoxifen treatment.
- Explore the correlation between genotypes/metabolites levels and clinical outcomes in terms of tumor relapse.
- Assess the feasibility, efficacy, and safety of concentration-guided adjustment of tamoxifen dosage in CYP2D6 poor metabolizers (PM).

Methods

Plasma levels of tamoxifen and its major metabolites:

UPLC triple stage tandem mass spectrometry (UPLC–MS/MS) method is under development and will be validated according to the FDA recommendations (**Figure 2**).

Pharmacogenomics:

Determination of CYP2D6 genotype (*3, *4, *5, *6 variant alleles), CYP2D6 phenotype (dextromethorphan test), CYP3A phenotype (midazolam test), and other cytochromes involved in the metabolism and drug transport.

Pharmacokinetic Modelling:

Characterisation of population pharmacokinetic profile of tamoxifen and its metabolites using classical non-linear mixed effects modelling techniques implemented in the NONMEM® software.

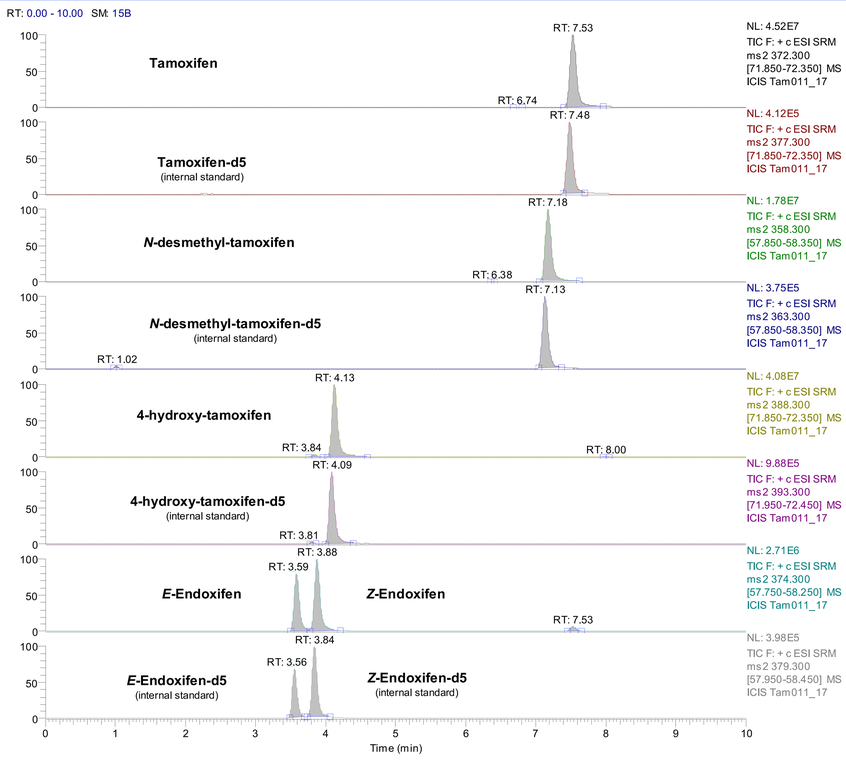

Figure 2. UPLC-ESI-MS/MS chromatogram of the highest calibration sample containing tamoxifen and its major metabolites. Corresponding deuterated analogues are used as internal standards.

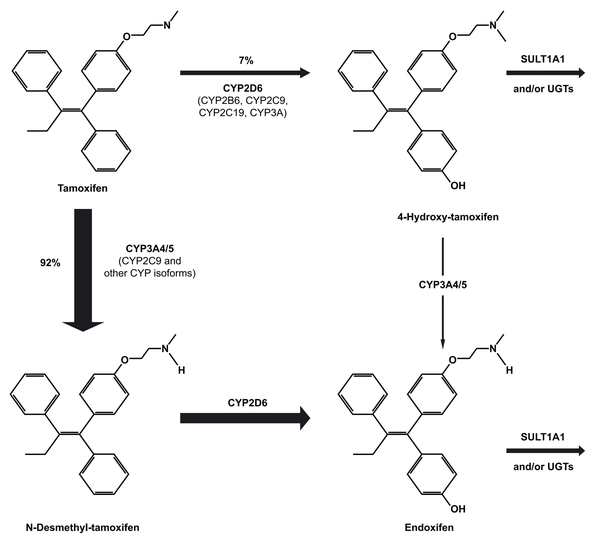

Figure 1. Biotransformation of tamoxifen and its metabolites. CYP3A4/5 is the major CYP isoform responsible for the formation of N-desmethyltamoxifen, whereas the generation of the more potent metabolites 4-hydroxytamoxifen and endoxifen (4-hydroxy-*N*-desmethyl-tamoxifen) are predominantly catalyzed by CYP2D6. Other CYP isoforms, including CYP2C19, CYP2C9, and CYP2B6, appear to play less important roles in tamoxifen metabolism in vitro. Phase II enzymes may also play a role in endoxifen clearance. SULT1A1: sulphotransferase 1A1; UGT: uridine diphosphate glucuronosyltransferase[5].

Patients inclusion criteria

- Hormone-sensitive breast cancer patients (defined as >10% estrogen receptor and/or >10% progesterone receptor positivity by immunohistochemistry).
- Patients treated with tamoxifen and eligible for exposure to higher doses.

Study design

- Interventional, open label phase III trial[9].
- 100 to 140 patients needed to be enrolled: until at least 10 poor-metabolizers, 10 intermediate-metabolizers and 20 extensive-metabolizers (**Figure 3**).

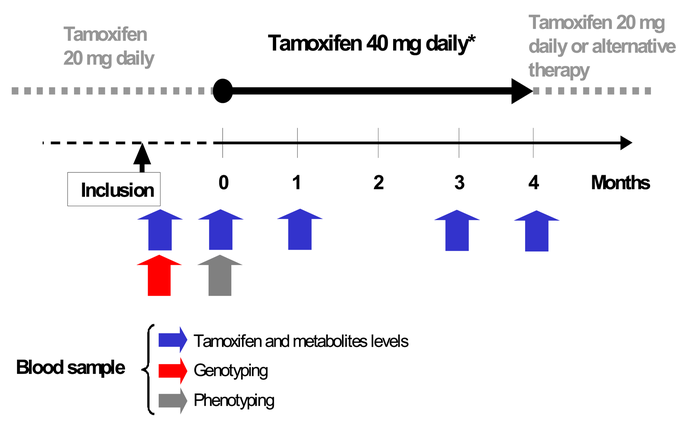

Figure 3. Study design. Patients receive tamoxifen (20 mg BID) daily for 4 months in the absence of disease progression or toxicity. Blood samples are collected for genotyping, phenotyping, and quantification of tamoxifen and its metabolites. The results of the CYP2D6 genotyping may be communicated to the patients who are PM, at the end of the 4 months and the opportunity of alternative endocrine therapy (e.g. Aromatase inhibitors) will be discussed.

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