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The effect of tamoxifen dose increment in patients with impaired CYP2D6 activity

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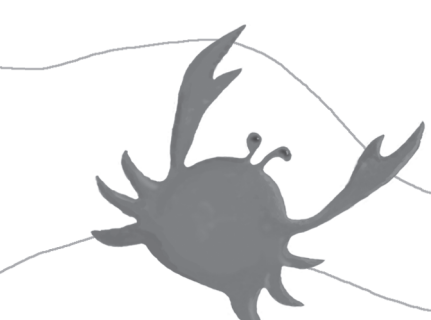

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ABSTRACT

Purpose The effect of a tamoxifen dose elevation on tamoxifen metabolite serum concentration was investigated in patients with a reduced CYP2D6 activity resulting from genetic variation and/or concomitant CYP2D6 inhibitor use. Additionally, baseline differences in endoxifen concentrations between the different CYP2D6 phenotypes were studied.

Patients and methods Breast cancer patients, treated with tamoxifen 20 mg QD for at least 4 weeks, were classified as phenotypic extensive (EM), intermediate (IM), or poor metabolizer (PM) based on their genotype and co-medication. In the patients with an IM or PM phenotype the tamoxifen dose was increased to 40mg QD for 4 weeks. Tamoxifen, 4-OH-tamoxifen, N-desmethyltamoxifen and endoxifen serum concentrations were measured at baseline and 4 weeks after the dose increment. Side effects of tamoxifen were assessed using the validated Functional Assessment of Cancer Therapy - Endocrine Symptom subscale (FACT-ESS-19).

Results The median baseline endoxifen concentration differed between EMs (11.4 µg/L: n=19), IMs (8.3 µg/L: n=16) and PMs (4.0 µg/L: n=7): p=0.040. Tamoxifen dose elevation significantly increased the median endoxifen levels in 12 IMs from 9.5 to 17.4 µg/L ($p<0.001$) and in 4 PMs from 3.8 to 7.8 µg/L (p=0.001), without influencing the median FACT-ESS-19 scores.

Conclusion Raising the tamoxifen dose to 40 mg QD significantly increased endoxifen concentrations in IMs and PMs without increasing side effects. The tamoxifen dose increment in PMs was insufficient to reach endoxifen levels equal to those observed in EMs, but may still be sufficient to increase tamoxifen efficacy. Future studies will clarify the direct effect of endoxifen exposure on tamoxifen efficacy and may reveal a threshold endoxifen level that is critical for its efficacy.

INTRODUCTION

Tamoxifen is a prodrug that needs to be metabolized by several enzymes of the cytochrome P450 (CYP) system into the more potent metabolites 4-hydroxy-tamoxifen (4-OH-tamoxifen) and 4-hydroxy-N-desmethyltamoxifen (endoxifen).[1-3] The CYP2D6 isoform is predominantly involved in the formation of endoxifen and to a smaller extent of 4-OH-tamoxifen. Both metabolites have a 50-fold higher affinity for the estrogen receptor than tamoxifen itself. During tamoxifen use the steady state plasma concentration of endoxifen is 5-10 fold higher than that of 4-OH-tamoxifen. Therefore, endoxifen is presumed to be mainly responsible for tamoxifen's clinical activity.[4-6] Tamoxifen is widely used for the treatment of patients with hormone receptor-positive breast cancer.[7, 8] Nonetheless, not all women with hormone receptor-positive breast cancer benefit from tamoxifen. The variability in tamoxifen response may partly be explained by individual differences in biotransformation of tamoxifen to the active metabolites. Alleles with frequent genetic variants of CYP2D6, encoding enzymes with low or absent CYP2D6 activity, are associated with lower endoxifen blood concentrations compared to the levels observed in patients with normal CYP2D6 activity.[5, 9] The CYP2D6 genotype may therefore impact tamoxifen efficacy. Additionally, concomitant use of CYP2D6 inhibitors may also impair tamoxifen efficacy. Antidepressants such as paroxetine and fluoxetine are strong CYP2D6 inhibitors that are commonly used to treat depression or hot flashes in tamoxifen treated breast cancer patients: prescription rates are 3-4 fold higher than in the general female population.[10]

The effect of CYP2D6 activity on tamoxifen efficacy has been indirectly studied by determining the effect of the CYP2D6 genotype and of concomitant CYP2D6 inhibitor use on tamoxifen treatment outcomes, but with inconsistent results.[3, 5, 9, 11-20] Therefore, genotyping for CYP2D6 is currently not part of the standard clinical management of breast cancer patients who are eligible for tamoxifen therapy. Additionally, no formal dose adjustments are recommended to patients who are concomitantly treated with a CYP2D6 inhibitor during tamoxifen treatment. Notably, the effect of endoxifen concentration on tamoxifen treatment outcome is uncertain, as results from well-designed prospective studies have not been reported yet. These studies are currently ongoing: CYPTAM (NTR1509) and CYPTAM-BRUT3 (NCT00966043).

We hypothesized that patients with a less active CYP2D6, based on the CYP2D6 genotype and/or concomitant CYP2D6 inhibitor use, will need an elevated dose of tamoxifen to compensate for the reduced formation of endoxifen. The aim of the current study is to investigate the effect of a tamoxifen dose increase from 20 to 40 mg QD on endoxifen serum concentration in patients with

a CYP2D6 poor (PM) or intermediate metabolizer (IM) phenotype. Additionally, we investigated the differences in endoxifen levels between the CYP2D6 phenotypes before dose escalation.

PATIENTS AND METHODS

Study population

Early or metastatic breast cancer patients (women ≥18 years) treated with tamoxifen 20mg daily (QD) for at least 4 weeks were eligible for study entry. All patients had adequate hematologic, renal, and hepatic functions. Concurrent cytotoxic chemotherapy or participation in a drug trial within 60 days prior to study entry was not allowed. Co-medication was allowed, if carefully monitored and registered. Co-medication was verified upon study entry by contacting the patients' community pharmacy. The protocol was approved by the institutional ethics committee of the Radboud University Nijmegen Medical Centre (Clinicaltrials.gov ID: NCT01192308). All patients gave written informed consent before entering the study.

CYP2D6 genotyping

Upon study entry all patients were genotyped for 33 CYP2D6 alleles (non-functional, reduced and normal activity alleles) using the Amplichip CYP450 test (Roche Diagnostics, Pleasanton, CA). Patients with more than two functional copies of the CYP2D6 gene were classified as ultrarapid metabolizers (UM). Patients with two functional alleles or one functional and one decreased activity allele were classified as extensive metabolizers (EM). Patients were classified as intermediate metabolizers (IM) if they had: a) one functional and one non-functional allele, b) one non-functional allele and one decreased activity allele or, c) two decreased activity alleles. Poor metabolizers (PM) were characterized by two non-functional alleles.

Dose intervention

After enrolment, EDTA blood was collected for CYP2D6 genotyping. Patients were classified as phenotypic EM, IM, or PM based on their CYP2D6 genotype and comedication.[21] Patients who used medication, known to inhibit CYP2D6, were phenotypically classified according to their endoxifen levels.[22] All patients with an IM or PM phenotype were instructed to increase their tamoxifen dose from 20 to 40mg QD for 4 weeks, except for those patients who experienced tamoxifen grade III/IV

adverse effects. Patients with an EM or UM phenotype did not participate in dose escalation and continued using tamoxifen 20 mg QD (Figure 9.1. CONSORT diagram).

Pharmacokinetic sampling and analysis

One serum sample was collected for each patient at baseline (study enrolment) and after 4 weeks of dose increment, if applicable. Serum samples were stored at -80°C. The serum concentrations of tamoxifen and its metabolites 4-OH-tamoxifen, N-desmethyltamoxifen and endoxifen were measured using liquid chromatographic- tandem mass spectrometry (LC-MS/MS) as described previously, with minor modifications.[23]

Safety

Blood samples for serum biochemistry and hematology were drawn at baseline, and at 4 weeks of dose increment, if applicable. Patients were interviewed about specific tamoxifen related adverse

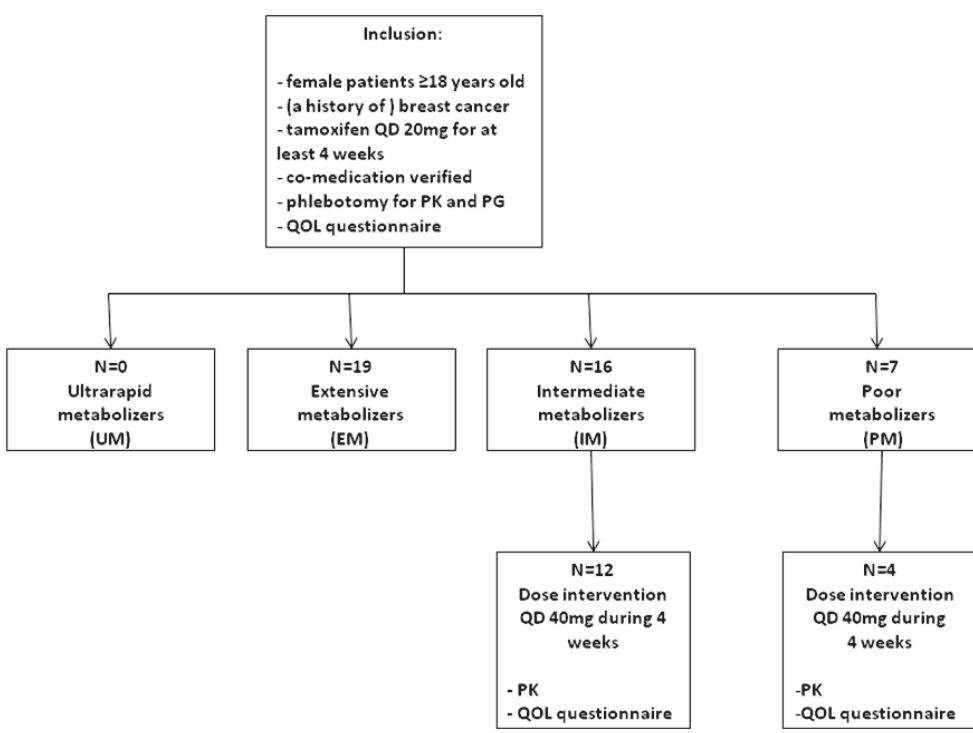

Figure 9.1 CONSORT diagram. EM, extensive metabolizer; IM, intermediatie metabolizer; PG, pharmacogenetics; PK, pharmacokinetics; PM, poor metabolizer; QD, once daily; QOL, quality of life; UM, ultrarapid metabolizer.

events such as headache, dizziness, nausea, vomiting, transpiration, rash, alopecia, muscle cramp, fluid retention and hot flashes. Side effects of tamoxifen were assessed using the validated Functional Assessment of Cancer Therapy - Endocrine Symptom subscale (FACT-ESS-19): patients filled in a questionnaire at baseline and at 4 weeks of dose increase, if applicable.[24] Scoring was based on an ordinal scale, in a range from 0 to 4 (0=no side effects). The maximum FACT-ESS-19 score is 76.

Statistical analysis and sample size considerations

The primary objective was to evaluate the effect of a tamoxifen dose increment from 20 to 40 mg QD during four weeks on endoxifen serum concentrations in patients with an IM or PM predicted CYP2D6 phenotype. A paired samples t-test on logarithmically transformed data was used to test for change in endoxifen concentration from baseline to four weeks of dose increment and for changes in FACT-ESS-19 score. A one-way ANOVA test on logarithmic transformed data was used to test for difference in endoxifen, tamoxifen, 4-OH-tamoxifen and N-desmethyltamoxifen concentrations and FACT-ESS-19 score at baseline among the three phenotype groups. An unpaired sample t-test on logarithmically transformed data was used to test for differences in endoxifen concentrations between EM vs. IM and EM vs. PM at baseline.

The sample size calculation for this study was based on data of Jin et al.[9] With a presumed increase in endoxifen concentration of 80% caused by the dose doubling and a standard deviation of 27 nM, eight subjects were required for dose escalation with a power (1-β) of 90% and a two-sided significance level (α) of 0.05. Unless noted otherwise, the Kruskal-Wallis test was used to evaluate baseline patient characteristics differences between phenotype groups. The statistical calculations were performed using SPSS 18 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Phenotyping and dose interventions

A total of 42 patients were enrolled in this study between August 2010 and February 2011. The CYP2D6 genotype and the serum concentration of tamoxifen, 4-OH-tamoxifen, N-desmethyltamoxifen and endoxifen were assessed at baseline. Based on the CYP2D6 genotype and concomitant CYP2D6 inhibitor use, phenotypical classification resulted in 19 EMs, 16 IMs and 7 PMs (based on the CYP2D6 genotype alone (n=4) and concomitant CYP2D6 inhibitor use (n=3; all with an EM genotype)).

The CYP2D6 inhibitors were escitalopram, citalopram and paroxetine. Patient characteristics are summarized in Table 9.1. Twenty-three patients (16 IMs and 7 PMs) were eligible for dose escalation from 20 to 40 mg QD during a period of 4 weeks. In 16 out of the 23 patients (12 IMs and 4 PMs) dose escalation was completed and pharmacokinetic assessment was repeated after four weeks (Figure 9.1). One of these patients was co-treated with escitalopram during dose escalation. Six dose

Table 9.1 Baseline characteristics (n=42), grouped by CYP2D6 phenotype

	CYP2D6 phenotype			
Characteristic	EM (n=19)	IM (n=16)	PM (n=7)	p
Median age (years)	56	56	57	0.920
Range	45-71	38-70	45-81	
Indication for treatment				
Adjuvant	16	14	7	
Palliative	3	2	0	
Median weight, (kg)	69.0	66.5	66.0	0.603
Range	54 - 107	55 - 112	58 - 75	
Median tamoxifen duration (months)	8.7	7.1	14.8	0.550
Range	0.9-57.3	1.1-29.9	3.0-32.8	
Median endoxifen conc. (µg/L)	11.4	8.3	4.0	0.040
Range	2.4-22.8	1.3-17.7	2.0-21.1	
Median tamoxifen conc. (µg/L)	140	93	122	0.244
Range	86 - 217	52 - 246	39 - 278	
Median N-desmethyltamoxifen conc. (µg/L)	211	191	264	0.544
Range	131 - 305	104 - 476	123 - 611	
Median 4-OH-tamoxifen conc. (µg/L)	2.0	1.7	1.7	0.232
Range	1.0 – 4.2	0.5 – 3.3	0.9 – 2.9	
CYP2D6 inhibitor use				
Total	0	0	3*	
Escitalopram			1	
Citalopram			1	
Paroxetine			1	
Menopausal status				
Premenopausal	4	2	1	0.860[&]
Postmenopausal	14	13	5	
Unknown	1	1	1	
Median FACT-ESS-19 score at baseline	62[$]	64	64[¥]	0.782

[&] Fisher's exact test

*All 3 patients using CYP2D6 inhibitors had a EM genotype

[$] Based on n=18 (one patient did not complete the questionnaire)

[¥] Based on n=6 (one patient did not complete the questionnaire)

Abbreviations: EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.

interventions were not carried out because of the following reasons: cessation of CYP2D6 inhibitor use, therefore reclassification to an EM phenotype (n=1); multiple adverse event on tamoxifen 20 mg QD (n=1); death prior to dose intervention (n=1); switch to an aromatase inhibitor prior to dose intervention (n=1); lost to follow up (n=2); loss of PK sample during transport (n=1).

Endoxifen concentration

The median endoxifen concentrations at baseline were significantly different between the EM (11.4 µg/L), IM (8.3 µg/L) and PM (4.0 µg/L) phenotype (p=0.040), which was mainly based on the difference between EMs and PMs (p=0.013), rather than on the difference between EMs and IMs (p=0.075), shown in Table 9.1 and Figure 9.2C. The three patients (EMs) using CYP2D6 inhibitors (escitalopram, citalopram and paroxetine) had baseline endoxifen concentrations of 4.0, 5.6 and 3.5 µg/L and were classified as PMs. The tamoxifen dose escalation from 20 to 40 mg QD resulted in a significant increase in the endoxifen concentrations in both IMs and PMs (p<0.001 and p=0.001, respectively: Table 9.2 and Figure 9.2). The median endoxifen levels increased from 9.5 to 17.4 µg/L in IMs and from 3.8 to 7.8 µg/L in PMs. The patient with the PM phenotype, based on escitalopram use, had a baseline endoxifen level of 4.0 µg/L, which increased to 7.3 µg/L after four weeks of 40 mg tamoxifen use. The median metabolic ratios (endoxifen/tamoxifen) at baseline and at 4 weeks are summarized in Table 9.2. At baseline, the metabolic ratio of the PM phenotype was low compared to the IM and EM phenotype. The dose intervention did not significantly change the metabolic ratios (Table 9.2).

Table 9.2 Median endoxifen concentrations and median metabolic ratios (endoxifen/tamoxifen) for three CYP2D6 phenotypes at baseline and after 4 weeks at 40mg QD

CYP2D6 Phenotype	No. evaluable after 4 weeks dose intervention	Median endoxifen conc. in µg/L (range)			Median metabolic ratio: endoxifen/tamoxifen		
		baseline	after 4 weeks at 40mg QD	p-value	baseline	after 4 weeks at 40mg QD	p-value
EM	19	11.4 (2.4-22.8)	n.a.	n.a.	0.083	n.a.	n.a.
IM	12	9.5 (3.4-17.7)	17.4 (6.1-22.8)	<0.001	0.088	0.087	0.446
PM	4	3.8 (2.0-21.1)	7.8 (3.5-42.1)	0.001	0.054	0.040	0.551

Abbreviations: EM, extensive metabolizer; IM, intermediate metabolizer; n.a., not applicable; PM, poor metabolizer.

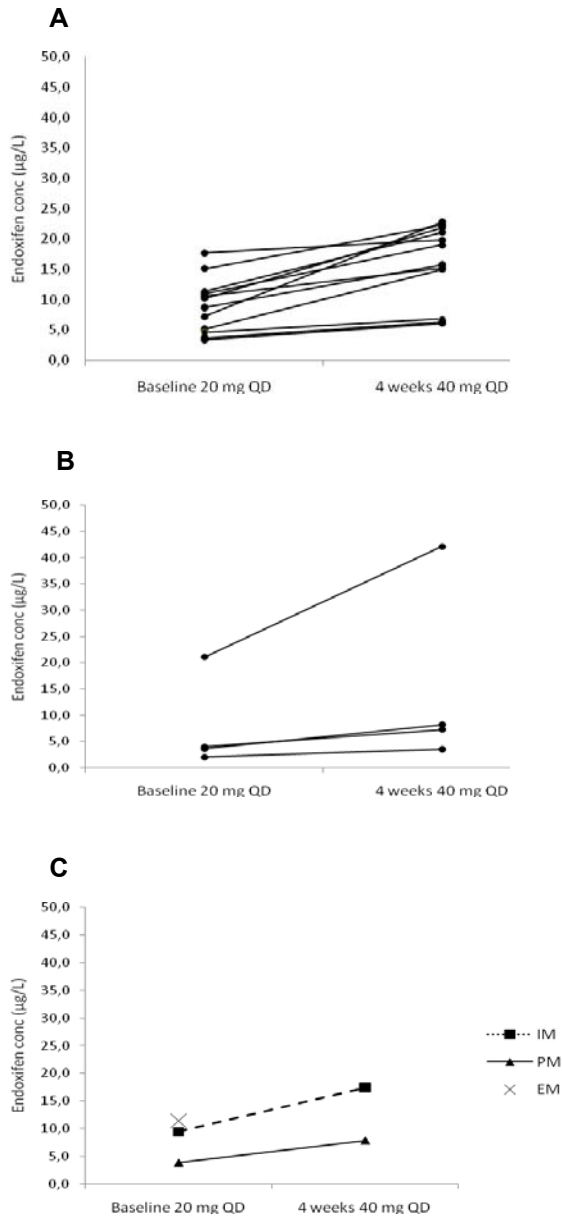

Figure 9.2 Influence of tamoxifen dose intervention on endoxifen concentration (µg/L) in individual phenotypical IM (**A**) and phenotypical PM (**B**). Influence of tamoxifen dose intervention on median endoxifen concentrations (µg/L) for two phenotypes (**C**). Abbreviations: EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; QD, once daily.

Table 9.3 Median FACT-ESS-19 scores at baseline and after 4 weeks at 40mg QD in dose intervention group

	Median FACT-ESS-19 score		
CYP2D6 phenotype	Baseline	After 4 weeks at 40mg QD	p
EM (n=19)	62[$]	n.a.	
IM (n=12)	62	63	0.762
PM (n=4)	55	61	0.214

[$] Based on n=18 (one patient did not complete the questionnaire)
Abbreviations: EM, extensive metabolizer; IM, intermediate metabolizer; n.a., not applicable; PM, poor metabolizer.

Toxicity and safety

The median FACT-ESS-19 scores at baseline and after 4 weeks of dose escalation are presented in Table 9.3. Baseline scores were not significantly different for EMs, IMs and PMs (p=0.782). The dose intervention had no influence on the FACT-ESS-19 scores. One patient experienced a serious adverse event (death due to intra-abdominal bleeding) and, although unlikely, the role of tamoxifen could not be ruled out. At the time of death the patient was using tamoxifen QD 20mg during 2.7 years and the dose intervention had not yet been executed. The baseline endoxifen concentration of this patient was 5.8 µg/L.

DISCUSSION

In this study we have demonstrated that a tamoxifen dose elevation from 20 to 40mg QD during 4 weeks resulted in a significant increase in endoxifen serum concentrations in breast cancer patients with an IM and PM CYP2D6 predicted phenotype, without increasing side effects. Like others, we noted a good correlation between baseline serum endoxifen concentrations and CYP2D6 genotype.[5, 9] Serum endoxifen concentrations were similar to the steady state endoxifen concentrations observed in a larger population (n=635) enrolled in a prospective study in the Netherlands and Belgium using the same LC-MS/MS method (CYPTAM NTR1509: EM 12.7 µg/L; IM 8.3 µg/L; PM 3.2 µg/L, unpublished results). The current endoxifen levels were also similar to those detected in other studies.[23, 25] The three patients (EMs) using CYP2D6 inhibitors (escitalopram, citalopram and paroxetine) had baseline endoxifen matching those of the PMs. However, both escitalopram and citalopram are considered weak CYP2D6 inhibitors, whereas our data suggest a moderate to strong inhibiting capacity.[22, 26] Comparably, venlafaxine was previously considered a weak CYP2D6 inhibitor.

Nonetheless, recent data were presented at the Annual San Antonio Breast Cancer Symposium 2012 showing a significant decrease in endoxifen levels as a result of concomitant venlafaxine use.[27] Our data, although limited to only two patients, stress the need to further elucidate the CYP2D6 inhibiting capacity of escitalopram and citalopram and consequently its potential detrimental effect on tamoxifen response. Based on the steady state endoxifen levels, these genotypic EM patients using escitalopram and citalopram were phenotypically classified as PM. It should however be noted that the endoxifen concentration without concomitant use of CYP2D6 inhibitors is unknown in these patients. Therefore, other reasons for the low endoxifen concentrations could not be ruled out.

Upon initiation of the current study, no information was available that tamoxifen dose escalation in women with impaired CYP2D6 activity might compensate for the reduced endoxifen exposure. Currently, three similar dose escalation studies have been reported, studying tamoxifen dose escalations of 30 mg QD,[28, 29] 40 mg QD[29] and 20 mg BID.[30] This is the first study however, to our best knowledge, in which a tamoxifen dose escalation from 20 to 40mg QD was applied in a breast cancer patient using a CYP2D6 inhibitor. In previous studies the dose intervention was driven by the CYP2D6 genotype or endoxifen levels, but patients using CYP2D6 inhibitors were not included.[28-30] Elevating the dose of tamoxifen in IM and PM patients resulted in more endoxifen being formed via either the not yet fully saturated CYP2D6 enzymes or by metabolism through other enzymes in the pathway. The unchanged metabolic ratio (endoxifen/tamoxifen) indicates that the balance between tamoxifen and metabolite is preserved, which might indicate that the metabolic pathways used are not altered when exposed to higher dosages of tamoxifen.

In the current study, endoxifen levels after dose escalation in IMs equaled the levels observed in EMs, which is consistent with the study results from Irvin et al.[30] Endoxifen levels in PMs after dose escalation were still lower than those observed in EMs. Nonetheless, the number of PM patients treated with an elevated dose was too small for formal comparison. Future studies should focus on dosing even higher than 40mg QD in PM patients (e.g. CYPTAM NTR1509) or using direct administration of the active metabolite endoxifen, thereby avoiding the complex metabolism of tamoxifen to endoxifen.[31]

There are some potential limitations of our study. For the pharmacokinetic assessments no trough samples were collected. The exposure to endoxifen however, was a result of the intake of tamoxifen during at least 4 weeks. Because the elimination half-life of tamoxifen is long (~5-7 days), of N-desmethyltamoxifen even longer (~14 days) and the elimination half-life of endoxifen is unknown, little differences are expected and observed between the minimal and maximal endoxifen concentrations measured directly after tamoxifen intake.[32, 33] This legitimates our approach. To

establish a new endoxifen steady-state concentration following dose escalation, a period longer than four weeks may be needed. Nevertheless, this study demonstrated that four weeks is a sufficient period of time to demonstrate a significant increase in endoxifen exposure, although the complete effect may not have been reached.

The current study was not designed to demonstrate improved treatment outcome resulting from the tamoxifen dose escalation. Although only ~39% of the interindividual variability in endoxifen concentrations can be explained by CYP2D6 genotype, low endoxifen concentrations have recently been associated with an increased risk of breast cancer events in tamoxifen treated early breast cancer patients.[25, 34] In this study by Madlensky et al. the 35% higher rate of breast cancer events was confined to the bottom quintile of the distribution, suggesting a threshold effect with a reported endoxifen threshold of 5.97 µg/L. Six (out of seven) PMs in our study had baseline endoxifen concentrations below this threshold, suggesting an increased recurrence risk and potential benefit from tamoxifen dose escalation.[34] In our study one PM had a baseline endoxifen concentration of 21.1 µg/L, which is significantly higher than the median endoxifen concentration in EMs and IMs. This exemplifies the large variance in endoxifen levels among the CYP2D6 phenotypes. Because the retrospective study by Madlensky et al. was not designed to investigate endoxifen efficacy and the difference in outcome between the patients with the lowest and higher endoxifen levels was borderline significant (HR=0.74; 95% CI, 0.55-1.00), these results should be interpreted with caution. Therefore, prospective studies are imperative to investigate the relation between endoxifen and clinical outcome. Subsequently, if such a relation is proven, prospective studies are needed to study the effect of tamoxifen dose escalation in patients with low endoxifen levels.

In conclusion, an elevation of the tamoxifen dose to 40mg QD increased endoxifen serum concentrations in IMs and PMs without increasing the side effects. The tamoxifen dose increment to 40mg in PMs was insufficient to reach endoxifen levels equal to those observed in EMs, but may still increase tamoxifen efficacy. Furthermore, the CYP2D6 inhibiting capacity of citalopram and escitalopram should be further explored, as we demonstrated similarity between endoxifen levels in PMs and in EMs who were co-treated with these antidepressants.

Acknowledgments

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