



Tailored Tamoxifen Treatment for Breast Cancer Patients: A Perspective

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Abstract

Tamoxifen, an endocrine agent, is widely used in the treatment of estrogen receptor-positive breast cancer. It has greatly reduced disease recurrence and mortality rates of breast cancer patients, however, not all patients benefit from tamoxifen treatment because in approximately 25% to 30% of the patients the disease recurs. Many researchers have sought to find factors associated with endocrine treatment outcome in the past years, however, this quest has not been finished. In this article, we focus on a factor that might influence outcome of tamoxifen treatment: interpatient variability in tamoxifen pharmacokinetics. In recent years it has become clear that tamoxifen undergoes extensive metabolism and that some of the formed metabolites are much more pharmacologically active than tamoxifen itself. Despite the wide interpatient variability in tamoxifen pharmacokinetics and pharmacodynamics, all patients receive a standard dose of 20 mg tamoxifen per day. Different approaches can be pursued to individualize tamoxifen dosing: genotyping, phenotyping, and therapeutic drug monitoring. Therapeutic drug monitoring seems to be the most direct and promising approach, however, further clinical research is warranted to establish the added value of individual dosing in tamoxifen treatment optimization.

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Introduction

Each year, approximately 1.4 million cases of breast cancer are diagnosed worldwide.¹ Approximately 70% of the breast cancers are estrogen receptor (ER)-positive; their growth is thought to be dependent on the binding of estrogen to the ER on tumor cells. Endocrine therapy forms the cornerstone of systemic treatment for women with ER-positive breast cancer at every stage of management and is directed against the growth-stimulating effects of estrogen on breast tissue. Endocrine agents abrogate estrogenic signaling via distinct mechanisms; either by impeding the transcriptional activity

of the ER or by diminishing estrogen synthesis. The most widely used endocrine agent is tamoxifen, which is used by pre- and postmenopausal women. Tamoxifen binds to the ER, leading to an altered receptor conformation and thereby prevents the binding of coactivators and inhibits transcription.² The development of aromatase inhibitors (AIs) has provided an alternative form of endocrine therapy. AIs suppress estrogen levels by inhibiting aromatase, the enzyme responsible for the synthesis of estrogens from androgenic substrates.³ Recently, these agents have become part of the standard treatment for most postmenopausal women with ER-positive breast cancer. For premenopausal women, guidelines dictate the use of adjuvant tamoxifen for 5 years and the recently published (ATLAS) and adjuvant Tamoxifen - To offer more? (aTTom) trials suggest use of tamoxifen for 10 years.^{4,5} The recommended adjuvant endocrine therapy in postmenopausal women is either an AI for at least 5 years, or sequential treatment with tamoxifen followed by an AI or vice versa. Despite improvements in recurrence rates and breast cancer mortality using these adjuvant therapies, approximately 25% to 30% of breast cancer patients have disease relapse within 10 years and will eventually die from the disease.⁶ This relatively high number of patients are at risk for side effects, but will not gain benefit of the endocrine treatment. Understanding the mechanisms underlying resistance is of importance to determine whether a patient is likely to benefit from

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the intended treatment. Many researchers have sought to find factors associated with endocrine treatment outcome, however, this quest has not been finished.⁷ It seems clear that there are several potential mechanisms by which resistance to endocrine therapy might evolve. These include variation in expression of the ER, modifications of the ER, increased levels or activity of ER coactivators, ER-independent growth because of additional activated growth factor signaling pathways, or stabilization of the ER despite the presence of tamoxifen.^{7,8} Apart from these tumor-related mechanisms, also patient-related factors might influence the response to endocrine therapy. In this article, we focus on a patient-related factor that might influence outcome of tamoxifen treatment: interpatient variability in tamoxifen pharmacokinetics.

Pharmacokinetics of Tamoxifen

The metabolism of tamoxifen leads to the formation of at least 22 phase I metabolites in humans.^{9,10} The main metabolic pathway involves demethylation, particularly by CYP3A4/5, to form *N*-desmethyltamoxifen, which is next hydroxylated by CYP2D6 to *N*-desmethyl-4-hydroxytamoxifen (endoxifen). To a smaller extent, tamoxifen is hydroxylated to form 4-hydroxytamoxifen, which is subsequently demethylated to endoxifen. This part of the biotransformation of tamoxifen is depicted in Figure 1. Tamoxifen is administered as a pure *zusammen* (*Z*)-isomer¹¹ and its metabolites are also generated primarily in the *Z*-form. There are large differences in the pharmacological activity of the tamoxifen metabolites, where (*Z*)-endoxifen and (*Z*)-4-hydroxytamoxifen are reported to have the highest antiestrogenic activity, being 30- to 100-fold more potent toward the ER than *N*-desmethyltamoxifen and tamoxifen itself.¹² (*Z*)-endoxifen is suggested to be the most

important metabolite, considering it is present at a steady-state serum concentration approximately 5 times higher than (*Z*)-4-hydroxytamoxifen in patients who use tamoxifen.¹³

The combination of wide interpatient variability in tamoxifen pharmacokinetics and large differences in biological activity of tamoxifen metabolites form the rationale for individual dosing of tamoxifen. At this time, however, all patients receive a standard dose of 20 mg tamoxifen per day. Different approaches can be pursued to individualize tamoxifen treatment; genotyping, phenotyping, and therapeutic drug monitoring (TDM). These 3 strategies will be discussed concisely herein.

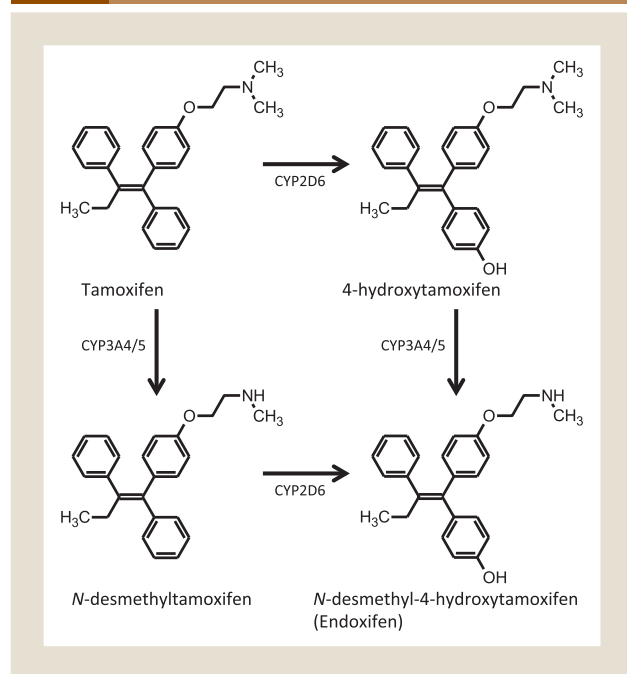
Approaches to Personalization of Tamoxifen Treatment

Genotyping

Based on the finding that the formation of (*Z*)-endoxifen predominantly depends on CYP2D6, genotyping patients for CYP2D6 polymorphisms has been suggested as a tool to individualize tamoxifen therapy. The CYP2D6 gene is known to be highly variable, caused by gene mutations or polymorphisms. Variations in the CYP2D6 gene can lead to CYP2D6 enzymes without, with diminished, or with increased catalytic activity. Based on the CYP2D6 enzyme activity, one can be categorized as a CYP2D6 poor metabolizer (no enzyme activity), intermediate metabolizer (diminished enzyme activity), extensive metabolizer (normal enzyme activity), or ultrarapid metabolizer (increased enzyme activity). Inactivating genetic polymorphisms in CYP2D6 are reported to be associated with lower (*Z*)-endoxifen levels¹⁵⁻¹⁷ and several studies showed an association between CYP2D6 genotype and recurrence-free survival.¹⁸⁻²¹ Other studies failed to show this association²²⁻²⁴ and recently, the large Arimidex, Tamoxifen, Alone or in Combination and Breast International Group 1-98 studies concluded that genetic variants of CYP2D6 are not predictive for outcome in tamoxifen-treated patients.^{22,25} However, the validity of these findings has been questioned.²⁶ Also, the large meta-analysis of the International Tamoxifen Pharmacogenomics Consortium, established to address the controversy regarding CYP2D6 status and tamoxifen treatment outcome, did not show a significant effect of CYP2D6 on tamoxifen treatment outcome in the entire heterogeneous study population.^{27,28} As a result, the value of genotyping to optimize tamoxifen treatment and dosing remains unclear.

Genotyping provides time-invariant information on the individual patient's metabolizing capacity. However, other factors such as nutrition, environmental factors and comedication are also known to affect tamoxifen pharmacokinetics. Of importance is the concomitant use of selective serotonin reuptake inhibitors that are commonly prescribed to patients who use endocrine therapy, to treat depression and to alleviate hot flash symptoms. This group of drugs, paroxetine in particular, is reported to possibly affect endoxifen levels by inhibition of CYP2D6.^{17,29,30} Another limitation of genotyping is that metabolite formation usually depends on multiple CYP enzymes, which is not taken into account when only 1 or 2 CYP genes are investigated. Also, the dependency on the polymorphisms that can be identified by the chosen genotyping assay is an important drawback. Moreover, the finding of new polymorphisms that affect CYP enzyme activity could possibly change the formerly-used classification and affect study results.

Figure 1 Part of the Biotransformation of Tamoxifen



Phenotyping

A phenotyping probe, a drug metabolized in a way similar to the target drug, can be used to predict the individual pharmacokinetic profile of the target drug. Using this approach, a combination of genotype and other factors that influence the metabolism, such as nutrition and comedication, are taken into account. Dextromethorphan was suggested as a possible phenotyping probe, and its serum levels were shown to be suitable to predict endoxifen exposure.³¹ Also, a ¹³C-dextromethorphan breath test could adequately predict endoxifen serum levels.³² However, both procedures are rather time-consuming and are somewhat cumbersome to predict endoxifen exposure. Moreover, although the metabolism of the probe and target drug are similar, they are never identical. Also, when comedication or other influencing factors change, the tamoxifen biotransformation can be affected and the initial phenotyping test results are no longer usable.

Therapeutic Drug Monitoring

Therapeutic drug monitoring, using actual measured drug concentrations instead of predictions of them, seems the most direct way to individualize tamoxifen treatment. With TDM, the combined result of all factors that affect tamoxifen pharmacokinetics, such as genotype, comedication, nutrition, and other (unknown) factors are measured. Also, TDM can be used to establish compliance, which is reported to be a point of concern in long-term tamoxifen treatment.³³ The wide interindividual differences in systemic exposure of endoxifen, a positive dose–exposure relationship^{13,15,16} and a positive exposure–efficacy relationship³⁴ form the rationale for application of TDM. The association between exposure and treatment outcome is the most important prerequisite for TDM. However, the essential role of tamoxifen metabolites was only suggested several years ago and clinical studies on treatment outcome take many years to complete. As a result, at this moment only 1 report to describe an association between metabolite concentrations and outcome has been published.³⁴ The Women's Healthy Eating and Living study was initiated to investigate the effect of a healthy diet on reduction of breast cancer events and early death in women with early-stage invasive breast cancer; the analysis of an association between active metabolite levels and outcome was secondary to the original hypotheses. A total of 1370 ER-positive breast cancer patients included in this study used tamoxifen and, after controlling for breast cancer stage and grade, a significant correlation between endoxifen serum levels in these patients and breast cancer outcome was found. The results of this study showed that patients with an endoxifen serum concentration > 5.9 ng/mL, 1096 included patients (80%), had a 26% lower recurrence rate than patients with a lower endoxifen serum concentration (hazard ratio, 0.74; 95% confidence interval, 0.55–1.00).³⁴ Indirect evidence for a dose–effect relationship originated from the Oxford Overview data, in which a significant test for trend was found for improved recurrence rates with increasing doses of adjuvant tamoxifen (20, 30, and 40 mg per day).⁶ Notably, the *in vitro* pharmacological modeling of (Z)-endoxifen for the treatment of ER-positive breast cancer showed that the anti-estrogenic effects of (Z)-endoxifen are concentration-dependent.^{14,35–37} Previous research has shown that most patients who receive a dose increase based on low (Z)-endoxifen levels when using a standard dose of

20 mg per day, are able to reach the threshold level when using 30 or 40 mg tamoxifen per day.¹³

Several studies on tamoxifen at different dose levels (20 vs. 30 or 40 mg per day) showed no significant difference in the frequency and severity of the experienced side effects, but did not report data on long-term serious toxicity.^{38,39} However, these studies included a relatively limited number of patients and no data on long-term serious toxicity, such as endometrial cancer, were reported. One report suggested a slightly greater risk of endometrial cancer with 40 mg tamoxifen per day, compared with 20 mg tamoxifen per day.⁴⁰

Because of the long half-life of tamoxifen and its metabolites,⁴¹ wide variability in serum concentrations of tamoxifen and its metabolites at steady-state during the day is not expected, therefore it is not required to obtain patient samples at specific time points. Furthermore, inpatient variability over several months is shown to be low,¹³ indicating that serum concentrations of tamoxifen and its metabolites are fairly constant during the steady-state phase of tamoxifen treatment. However, a patients' comedication and nutrition can change over time; obtaining TDM samples on a regular basis will be of value to monitor the effects of these factors on metabolite levels.

Future Perspectives

At this moment, TDM seems the most direct and promising approach to tailor tamoxifen treatment. However, incontrovertible evidence for an exposure–outcome relationship is lacking at this point in time. Also, the complex metabolism of tamoxifen leads to the formation of multiple metabolites, with different pharmacological activities. In recent years, the focus has been on the tamoxifen metabolite endoxifen, however, the contribution of other metabolites to treatment outcome cannot be ruled out. A possible strategy to investigate this could be to establish an Antiestrogenic Activity Score (AAS) based on *in vitro* activity of different metabolites, as suggested by Barginear et al.¹⁵ and to correlate this score with treatment outcome.

To investigate the added value of TDM in treatment efficacy, a randomized prospective clinical trial is warranted. A possible study design could be to randomize patients who are about to start adjuvant tamoxifen therapy into 2 groups; group 1 starts with 20 mg tamoxifen per day, according to standard of practice, and a TDM sample is obtained every 3 months. Based on the analyzed metabolite levels, these patients are advised to increase their daily dose to 30 or 40 mg tamoxifen per day. At this time, the suggested serum concentration threshold of 5.9 ng/mL endoxifen could be used, until more study results to suggest a certain threshold or show the value of an AAS become available. The control group receives 20 mg tamoxifen per day, according to standard of practice and receives no dose adjustment. Another option would be a case-control design, in which patients for whom TDM was used to optimize the treatment are matched to 3 patients for whom TDM was not used. When these patients are matched regarding prognostic factors and date of diagnosis, the difference in recurrence-free survival can be analyzed.

Recently, a dried blood spot (DBS) method for the quantification of tamoxifen and (Z)-endoxifen was developed.^{42,43} With DBS sampling, a sample is obtained using a finger prick method and

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drops of blood are collected on a DBS card. The use of DBS sampling in a prospective clinical trial enables easier logistics; the patient can self-sample at home and there is no need for a phlebotomist. Furthermore, samples can be transported using regular mail service and stored at room temperature, because no special transport and storage conditions are required.

Conclusion

Individualization of tamoxifen treatment based on active metabolite levels might be of value to optimize tamoxifen treatment. However, further clinical research is highly warranted to establish the role of active metabolite levels in tamoxifen treatment optimization.

Disclosure

The authors have stated that they have no conflicts of interest.

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