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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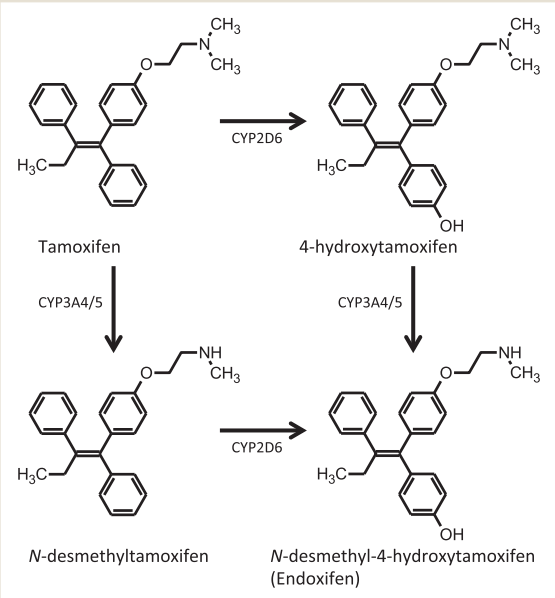
the intended treatment. Many researchers have sought to find factors associated with endocrine treatment outcome, however, this quest has not been finished.[7] It seems clear that there are several potential mechanisms by which resistance to endocrine therapy might evolve. These include variation in 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*)-isomer[11] 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]

Figure 1 Part of the Biotransformation of Tamoxifen



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 levels[15-17] and several studies showed an association between CYP2D6 genotype and recurrence-free survival.[18-21] Other studies failed to show this association[22-24] 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.