

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Update on CYP2D6 and Its Impact on Tamoxifen Therapy

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H&O What is CYP2D6? What is its significance in regard to tamoxifen and breast cancer?

MG Cytochrome P450 enzymes are involved in the metabolism of both exogenous and endogenous compounds. Cytochrome P450 2D6 (CYP2D6) is an enzyme present within the liver and other tissues; it is responsible for the metabolism of approximately 10–20% of drugs. In the case of tamoxifen, CYP2D6 (and other enzymes) are involved in the oxidation of the parent drug to an active metabolite, referred to as *4-hydroxytamoxifen*. However, more than 90% of tamoxifen undergoes CYP3A-related hepatic metabolism to N-desmethyltamoxifen, the most abundant tamoxifen metabolite. Therefore, 4-hydroxytamoxifen is considered a minor metabolite. CYP2D6 is the primary enzyme involved in the oxidation of N-desmethyltamoxifen to 4-hydroxy-N-desmethyltamoxifen, referred to hereafter as endoxifen. These 2 hydroxylated metabolites—4-hydroxytamoxifen and endoxifen—are substantially more potent in terms of their ability to bind to the estrogen receptor (ER), with potency similar to estradiol, whereas tamoxifen and N-desmethyltamoxifen are much weaker antagonists. The hypothesis, therefore, has been that the concentrations of these hydroxylated metabolites may be important in tamoxifen-treated patients and may affect drug-related phenotypes such as side effects and breast cancer recurrence.

Investigators within the Consortium on Breast Cancer Pharmacogenomics (COBRA) were some of the first to study CYP2D6 and endoxifen; these investigators characterized endoxifen's anti-estrogenic activity, and established that CYP2D6 was the most important enzyme in the formation of endoxifen. In 2003, Stearns

and colleagues reported that genetic variation and potent inhibitors of the CYP2D6 enzyme system were associated with lower endoxifen concentrations. Individuals referred to as CYP2D6 poor metabolizers inherit genetic variants associated with little or no CYP2D6 activity, and these patients appear to have the lowest endoxifen concentrations.

Another important finding to come out of studies was that although 4-hydroxytamoxifen was previously thought to be the most important tamoxifen metabolite, the plasma concentrations of 4-hydroxytamoxifen were low—in the range of between 5 and 10 nM—whereas the concentration of endoxifen had much wider variability, ranging from 10–180 nM. Therefore, endoxifen can be considered the most abundant active metabolite.

H&O Does current evidence suggest testing for CYP2D6?

MG There have been various studies evaluating CYP2D6 and its effect on outcome, but the findings have been incongruous.

We were one of the first groups that looked at the relationship between genetic variability in tamoxifen metabolizing enzymes and clinical outcomes. In the 1980s, Dr. James Ingle conducted a North Central Cancer Treatment Group (NCCTG) prospective trial evaluating tamoxifen as an adjuvant therapy for breast cancer. The study population consisted of postmenopausal women with estrogen receptor (ER)-positive breast cancer that had been surgically resected; the patients received 20 mg/day of tamoxifen for 5 years as an adjuvant therapy to reduce the risk of recurrence. In 2005, we reported a retrospective analysis of this clinical trial and demonstrated an association between the CYP2D6 *4 genetic variant and a higher risk of breast cancer recurrence and lower risk of hot flashes. Subsequently, we published a follow-up

study with Dr. Hiltrud Brauch's group out of Stuttgart Germany in 2009. In this study, we conducted more comprehensive CYP2D6 genotyping in patients enrolled in the NCCTG study and pooled the data along with a similar population of patients from Germany with early stage breast cancer treated with tamoxifen (total 1,325 patients). In this analysis, CYP2D6 poor metabolizers had approximately a 2-fold higher risk of recurrence compared to extensive metabolizers.

In a separate validation study that we conducted in collaboration with the Austrian Breast and Colorectal Study Group (ABCSG 8) and reported at the San Antonio Breast Cancer Symposium (SABCS) in 2008, we demonstrated an association between CYP2D6 genetic variability and disease-free survival. In the parent trial, women with ER-positive breast cancer who had surgery were randomized to receive tamoxifen for 5 years or tamoxifen for 2 years and then switch to an aromatase inhibitor (anastrozole). We reported that women who were CYP2D6 poor metabolizers had a higher risk of recurrence compared to extensive metabolizers. Interestingly, CYP2D6 poor metabolizers who switched to anastrozole did not have an increased risk of recurrence, confirming prior data that CYP2D6 is not involved in the metabolism of aromatase inhibitors.

There have been a number of studies that have not corroborated this relationship. The largest negative study was reported by the International Tamoxifen Pharmacogenomics Consortium (ITPC), originally started by investigators from the Pharmacogenetics Research Network. The purpose of the ITPC was to establish a worldwide experience with regard to tamoxifen and CYP2D6. In a preliminary report that I presented on behalf of the ITPC at SABCS in 2009, there was no association between CYP2D6 genetic variability and tamoxifen outcome. However, because of the substantial number of patients with data on only one CYP2D6 allele (*4) and lack of evidence regarding CYP2D6 inhibitors, this report and other negative studies have led to discussions about study design.

There are also many studies reporting on the association between CYP2D6 inhibitors and tamoxifen treatment outcome. Some of these studies found that coadministration of potent CYP2D6 inhibitors along with tamoxifen was associated with a higher risk of recurrence. Conversely, other studies have not demonstrated an association.

Overall, the contradictory findings have caused a great deal of confusion. While many clinicians in the oncology community recommend against using potent CYP2D6 inhibitors, most are unsure about testing for the genetic component (CYP2D6 genotyping) given the conflicting data.

The American Society of Clinical Oncology has published guidelines on the use of endocrine therapy for the treatment of postmenopausal women with hormone

receptor-positive breast cancer. An update to the clinical practice guidelines was published in the July 12 issue of *Journal of Clinical Oncology*. These guidelines specifically address the controversy surrounding CYP2D6 and tamoxifen; they do not recommend testing for CYP2D6 genotype prior to tamoxifen use, but suggest that clinicians avoid potent inhibitors of the CYP2D6 enzyme system.

H&O Do you foresee CYP2D6 genotyping becoming a companion diagnostic in the future?

MG As we obtain more data from large randomized trials of tamoxifen, CYP2D6 genotype testing may eventually become a companion diagnostic. There are, however, several barriers to overcome as we study the pharmacogenetics of tamoxifen and other oral therapies. Perhaps the main barrier is that studying the genetic basis for pharmacokinetic variability of oral drugs is difficult if patients are not taking the drug. There are emerging data demonstrating that adherence is poor in patients taking long-term oral endocrine therapies, and up to 50% are nonadherent to the 5-year course of therapy. Interestingly, CYP2D6 enzyme activity has been associated with poor adherence to oral therapy, with some data from the COBRA group suggesting that CYP2D6 extensive metabolizers (compared to poor metabolizers) are more likely to discontinue drug therapy because of side effects. It is for this reason that validation studies evaluating biomarkers that are potentially predictive of drug benefit should be performed in the context of clinical trials.

Another unresolved issue is whether variation in the enzymes responsible for the conjugation of tamoxifen and its metabolites affect tamoxifen drug response phenotypes. Since conjugation by the UDP-glucuronosyltransferase (UGT) enzymes appears to negate the anti-estrogenic activity of the hydroxylated metabolites, genetic and drug-induced variation in the UGTs may account for the additional variability in tamoxifen pharmacokinetics and clinical activity.

Finally, with an ever-increasing number of new cancer therapies (eg, chemotherapy, trastuzumab, or aromatase inhibitors) that are prescribed before, along with, or after tamoxifen, respectively, CYP2D6 enzyme variability may not be associated with breast cancer recurrence in those clinical scenarios where other active therapies are prescribed along with tamoxifen. It is for these reasons that the research community should study the pharmacogenetics of tamoxifen in women who receive the drug as monotherapy.

H&O What treatment options are available for pre- and postmenopausal women with breast cancer?

MG Postmenopausal women have 2 therapeutic options: tamoxifen and one of the third generation aromatase

inhibitors. Upfront use of an aromatase inhibitor for 5 years is superior to 5 years of tamoxifen in terms of recurrence-free survival, but not overall survival. So, while one question has been whether tamoxifen-treated women who are CYP2D6 poor metabolizers have a higher risk of recurrence, another research question (still unanswered) is whether women who are CYP2D6 extensive metabolizers would do as well on tamoxifen as on aromatase inhibitors.

In the premenopausal adjuvant setting we still do not know whether women should be treated with an aromatase inhibitor. A trial conducted in Europe (ABCSG 12) evaluated either tamoxifen or an aromatase inhibitor in premenopausal women with ER-positive breast cancer. In this study, all women were treated with ovarian function suppression. Although the initial report showed similar outcomes between the 2 groups in terms of recurrence, the updated data demonstrated that the group randomized to aromatase inhibitors had a significantly higher risk of death compared to those treated with tamoxifen. There are no data regarding the role of CYP2D6 in premenopausal women taking tamoxifen.

H&O What are the implications of concurrently administering tamoxifen with agents such as selective serotonin reuptake inhibitors (SSRIs)?

MG As I mentioned earlier, the data that are available are contradictory, as some studies have suggested an association between the use of potent CYP2D6 inhibitors and breast cancer recurrence, and other studies have not demonstrated an association. Most clinicians are in agreement that potent inhibitors, such as paroxetine, should be avoided in women taking tamoxifen, especially since alternative drugs can be used.

We are currently conducting a prospective clinical study with collaborators at the University of Michigan, Johns Hopkins, Indiana, and US Oncology, in which we are evaluating whether SSRIs and serotonin-norepinephrine reuptake inhibitors such as citalopram, venlafaxine, and escitalopram affect endoxifen concentrations in women chronically taking tamoxifen. We believe this question is important, as these drugs are commonly coprescribed with tamoxifen to treat hot flashes, and there are few data regarding the effect of these drugs on endoxifen concentrations.

H&O Are there any ongoing studies?

MG There are large retrospective studies evaluating the pharmacogenetics of tamoxifen and aromatase inhibitors in premenopausal women. One such study is SOFT (Suppression of Ovarian Function Trial; IBCSG24-02).

This phase III trial is evaluating the role of ovarian function suppression and exemestane and tamoxifen as adjuvant therapies for premenopausal women with endocrine-responsive breast cancer. Another pharmacogenetic analysis is taking place in TEXT (Tamoxifen and Exemestane Trial; IBCSG25-02).

In the postmenopausal setting, there are a number of ongoing retrospective analyses from the large clinical trials that compared tamoxifen to aromatase inhibitors, and we expect data soon. As mentioned previously, the ITPC has been established to collect and analyze data from multiple different studies across the world with regard to CYP2D6 and tamoxifen outcome, and final data from this group are expected in early 2011. Finally, in the United States, there is an ongoing prospective trial in patients with metastatic breast cancer treated with tamoxifen (ECOG E3108) led by Dr. Stearns from Johns Hopkins. This trial is prospectively evaluating whether CYP2D6 enzyme activity and endoxifen concentrations are associated with time to progression.

While the studies surrounding the metabolism of tamoxifen have given us a glimpse of the potential importance of endoxifen, an obvious question is whether the primary administration of endoxifen could lead to superior clinical outcomes for women with ER-positive breast cancer. We are currently collaborating with the National Cancer Institute (NCI) to develop endoxifen as a drug for the treatment of ER-positive breast cancer. The NCI has synthesized endoxifen hydrochloride, and hopes to complete preclinical pharmacology and toxicology studies later this year. Phase I endoxifen studies will commence at the NCI and Mayo Clinic in 2011.

Suggested Readings

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