Tamoxifen, Endoxifen, and CYP2D6: The Rules for Evaluating a Predictive Factor

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In the post–Human Genome Project era, “personalized medicine” has become a buzzword. Health-care professionals increasingly have access to gene sequence data, with the promise that this information will improve the health of the individual. In the area of breast oncology, the study of genetic markers associated with clinical outcome has been a relative success story.

In the post–Human Genome Project era, “personalized medicine” has become a buzzword. Health-care professionals increasingly have access to gene sequence data, with the promise that this information will improve the health of the individual. In the area of breast oncology, the study of genetic markers associated with clinical outcome has been a relative success story. While classic tumor-related factors such as size, grade, and nodal status are still used, researchers have increasingly focused on studying genome-wide genetic variation, both at the level of the tumor and the host, with the goal of identifying subsets of patients at lower or higher risk for disease recurrence. Many of these biomarkers represent classic “prognostic factors,” or markers associated with the biology of the disease.

Prognostic vs Predictive Factors

In contrast to a prognostic factor, a predictive factor identifies a subgroup of patients more or less likely to respond to an intervention, such as drug therapy. The study of genetic predictive factors in drug therapy is often referred to as pharmacogenomics, or the study of the relationship between specific DNA-sequence variation and drug effect. The importance of pharmacogenomics in oncology cannot be overemphasized, wherein variation at the level of genes encoding enzymes that catalyze phase I and II drug metabolism, drug transporters, drug receptors, and drug targets can lead to marked differences in the frequency of treatment toxicity or treatment failure. Given the increasing number of pharmaceuticals approved for a given disease type, the ability to “personalize” therapy based on inherent genetic variation at the level of the host or the tumor genome is the ultimate promise of pharmacogenomics.

An obvious choice for personalization of drug therapy would be the adjuvant hormonal therapy of estrogen receptor (ER)-positive breast cancer. While tamoxifen and the aromatase inhibitors exhibit different mechanisms by which they abrogate or disrupt ER activity, randomized trials comparing tamoxifen with the third-generation aromatase inhibitors in the adjuvant treatment of breast cancer demonstrated only a small but statistically significant improvement in disease-free survival in favor of anastrozole (Arimidex) and letrozole (Femara).[1,2] which did not translate into a survival advantage, as confirmed in a recent meta-analysis.[3] Therefore, the identification of a biomarker unique to either drug metabolism or the mechanism of action of either drug would provide an opportunity for “individualization.”

Role of Tamoxifen Metabolites

As extensively reviewed in the article by Kuderer and Peppercorn, the initial hypothesis underlying tamoxifen pharmacogenomics was that the relative concentrations of tamoxifen and its metabolites may have clinical relevance. This was based on evidence for marked differences in ER binding as well as inhibition of estrogen-stimulated growth, comparing tamoxifen with the hydroxylated metabolites.[4-6] While the potent 4-hydroxylated metabolite of tamoxifen—4-hydroxytamoxifen—continues to be used by researchers as an in vitro surrogate for tamoxifen activity, human tamoxifen pharmacokinetic data has not supported a major role for 4-hydroxytamoxifen, given that steady-state plasma concentrations are very low (< 10 nM).[7] However, the recent identification and characterization of another hydroxylated tamoxifen metabolite—endoxifen—has led to the hypothesis that endoxifen may contribute substantially to the
overall activity of tamoxifen in humans. Like 4-hydroxytamoxifen, endoxifen is approximately
100-fold more potent as an antagonist of the ER than the parent drug, tamoxifen.[5] New data
suggest that endoxifen but not 4-hydroxytamoxifen results in ER-alpha degradation in addition to its
effects on the ER at the level of transcription.[6] A prevailing theory raised by Kuderer and
Peppercorn (and others) is that the ER is “saturated” by tamoxifen (thereby nullifying any biologic
differences in receptor-binding affinity). However, Wu et al demonstrated that the in vitro
mechanism by which endoxifen blocks ER-signaling and its effect on proliferation is dose-dependent
(not occurring at concentrations seen in human CYP2D6 poor metabolizers) and importantly occurs
even in the presence of clinically relevant concentrations of tamoxifen and 4-hydroxytamoxifen.[6]

Further Importance of Endoxifen

Endoxifen is formed by the CYP2D6-mediated oxidation of N-desmethyltamoxifen.[5,8] Thus,
common genetic variation in the gene encoding CYP2D6 and/or drug-induced inhibition of CYP2D6
enzyme activity significantly reduces endoxifen concentrations in humans[9] and is associated with
an increased risk of recurrence in some but not all studies, as reviewed by Kuderer and Peppercorn.
In a new study involving over 1,300 patients, Schroth, Goetz, et al confirmed the association
between CYP2D6 genetic variation and clinical outcomes.[10] Furthermore, the absolute difference
between extensive and poor metabolizers in the proportion of patients who relapsed was 6.7% at 5
years and 13.4% at 9 years. The magnitude of this effect corresponds to an unadjusted hazard ratio
(HR) of 2.12, which was significantly larger than the HR of tamoxifen relative to anastrozole (1.31) in
the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial[2] and suggested that there would be
little difference between tamoxifen-treated CYP2D6 extensive metabolizers and those receiving
anastrozole.[10]

Based on the extensive preclinical and clinical findings regarding the importance of endoxifen, the
National Cancer Institute is currently developing endoxifen as a primary drug for the treatment of
ER-positive breast cancer, including production of clinical-grade endoxifen hydrochloride and
preclinical toxicology/pharmacology for IND submission. The first human studies are expected to
commence in 2010.

Evaluation Problems

An important question remains as to why there has been so much confusion regarding the
pharmacogenetics of tamoxifen when the underlying scientific principles appear biologically sound. A
brief review of the “rules” for evaluating predictive markers in the context of retrospective studies
may provide insight on this matter.

First, in the case of drug therapy, a predictive factor is first and foremost associated with the
delivery of a drug. So, it follows that one must document whether the drug was administered
(adherence) before beginning to ponder the role of a biomarker. While this is less of a problem with
studying intravenous medications (since delivery of a drug can be documented), for oral therapy,
there is no guarantee that the drug will be delivered at the dose/schedule it was prescribed once the
patient leaves the clinic. Notably, suboptimal adherence to drug therapy has been observed in up to
40% of individuals taking adjuvant hormonal therapy,[11-13] and nonadherence has been associated
with higher rates of death.[14] While pharmacologists would not begin to consider the results of a
pharmacokinetic study if a significant number of the subjects were nonadherent to the
recommended dose and schedule, many researchers studying predictive factors are “in the dark”
regarding adherence to drug therapy. This is one reason why retrospective analyses of predictive
markers are better evaluated in the context of clinical trials, as adherence is generally accounted for
and patients can be censored when they stop therapy.

In the case of tamoxifen and CYP2D6, following the publication of data suggesting that CYP2D6
genotype may be associated with hot flashes,[15] Rae et al demonstrated that patients with higher
CYP2D6 enzyme activity (eg, extensive metabolizers) had higher rates of drug discontinuation.[16]
Therefore, the development of tamoxifen-related side-effects such as hot flashes, which have been
associated with improved clinical outcomes,[17] and which are mediated in part by CYP2D6-related
bioactivation of tamoxifen, may affect adherence to tamoxifen therapy.

Another substantial epidemiologic problem is difficult to account for when studying genetic
variation of drug metabolism enzymes is the role of the environment. In the case of tamoxifen, the
CYP2D6 enzyme is commonly inhibited by medications that are co-prescribed to ameliorate hot
flashes as well as depression. For example, the administration of a potent CYP2D6 inhibitor to a
tamoxifen-treated extensive metabolizer results in endoxifen concentrations that are similar to those
seen in genotypic poor metabolizers.[5] This issue is of particular concern, since patients most likely to receive a potent CYP2D6 inhibitor are CYP2D6-genotypic extensive metabolizers, who are more likely to experience hot flashes.

While it should be noted that nearly all of the “negative” retrospective studies regarding tamoxifen and CYP2D6 have been substantially underpowered, there is the additional weakness that is associated with the retrospective design, related to the lack of a surveillance schedule and the documentation needed to verify disease progression. This leads to large numbers of patients who cannot be located, leading to uncertainty regarding the number of patients experiencing disease progression as well as death without progression. While it should be clear that the documentation needed to confirm the absence of disease progression is as vital as confirming disease progression, most retrospective studies do not have access to patient follow-up to make this determination.

While prospective cohort studies are indeed an improvement over retrospective studies, a point should be made regarding the timing of collection of genetic material. If genetic material (eg, derived from a blood or buccal sample) is collected months or years after breast cancer surgery, patients with early recurrence would be excluded from analysis, leading to the introduction of survival bias. This issue is of great importance when studying biomarkers in tamoxifen-treated patients, as studies have consistently demonstrated a peak in the hazard rates for recurrence during the first 2 to 3 years of adjuvant tamoxifen therapy.[18]

Conclusions

After a careful review of the evidence as outlined by Kuderer and Peppercorn, the question that must be answered is whether the data are robust enough to consider the role of CYP2D6 when prescribing tamoxifen. Should clinicians withhold CYP2D6-inhibiting medications while ignoring the silent genetic polymorphisms that reduce CYP2D6 enzyme activity? Kuderer and Peppercorn are correct that more data are needed; however, patients should be made aware of the data regarding the importance of CYP2D6-mediated metabolism of tamoxifen.

Furthermore, in addition to discontinuation of potent CYP2D6 inhibitors, postmenopausal patients about to begin tamoxifen therapy should be considered for CYP2D6 testing, and CYP2D6 poor metabolizers should be considered for alternative therapies such as an aromatase inhibitor. For those who are unable to discontinue potent CYP2D6 inhibitors, an alternative hormonal therapy (eg, aromatase inhibitor) should be considered. In contrast to the postmenopausal setting, where much of the data in regard to tamoxifen and CYP2D6 have been generated, CYP2D6 genotyping should not be considered routine in the premenopausal, prevention, or ductal carcinoma in situ settings, given the lack of substantive data and approved alternatives in these settings.

References:


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