Pharmacogenomics in the Clinic: New Questions About Tamoxifen

To the Editor: I enjoyed the excellent summary of recent insights regarding tamoxifen's pharmacogenomics,¹ its essential activation to endoxifen by CYP2D6, the poor metabolizer (PM) phenotypes that cannot perform this step, and the unintended blockade of this activation by commonly prescribed drugs.² The study of North Central Cancer Treatment Group (NCCTG) tissues showing a marked survival decrement for PM phenotypes³ is rich with implications for practice. Additionally, one can't help but grin at the authors' assiduously politically correct way of handling the use of selective serotonin reuptake inhibitors (SSRIs) to treat hot flashes, a colossal therapeutic misadventure for breast cancer patients in retrospect. After all, it is remarkable how many ways we shoot ourselves in the foot, proverbially speaking. Yet application of these new insights promises better results from tamoxifen. Have we arrived at the threshold for routine pharmacogenomic testing?

Some provocative issues were not addressed by the authors. First, the science is either retrospective or based on relatively few patients. But would it be ethical to study the questions of genotype and drug interaction in a large, prospective, controlled trial? Such a trial would stipulate a control group with survival outcomes of 1980s placebo groups. Arguably, clinicians don't need absolute scientific rigor to practice common-sense medicine. Limited although compelling anecdotal or scientific observations akin to the admonition against putting one's finger in the electric socket can suffice for adopting a pharmacogenetic approach to endocrine therapy without a prospective trial.

The weightiest questions spawned by tamoxifen's pharmacogenomics pertain to the aromatase inhibitors (AIs). Eliminate PMs and those taking CYP2D6 inhibitors from randomized AI studies: Would there still be an advantage for AIs? One would anticipate that endoxifen-poor patients make up the lion's share of treatment failures among the tamoxifen-treated control arms, and that therapeutic outcomes could be equivalent for appropriately selected and coached (i.e., instructed not to take 2D6 inhibitors) patients receiving tamoxifen. By extension, absence of a survival disadvantage for patients who generate sufficient endoxifen would raise reservations about the skeletal consequences of AIs, especially in low-risk women. Moreover, appropriately selected premenopausal women would not be missing out on the benefit of AIs, the common exclusionary wince for estrogen receptor-positive premenopausal women. Possibly, such a re-evaluation of the AI data could end up reaffirming tamoxifen's central role, PMs and SSRI users aside.

References

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Conversely, the decision to avoid AIs would be inappropriate for patients who cannot get by without an SSRI or for PMs.

Hopefully, this work on PMs will spur new correlative science initiatives in already completed trials and in those currently underway. This represents a challenge for the vested interests of companies who sell AIs, and provokes a question of whether society can pursue questions that are clinically necessary but potentially adverse to industry. Most likely, the U.S. Food and Drug Administration's leadership will be needed to compel such inquiries, particularly since AI commercial licensing has long been a done deal.

Should all patients considered for endocrine therapy and prevention of breast cancer be tested for the CYP2D6 PM polymorphisms? In the white population, 5% to 10% of patients unable to derive a benefit from tamoxifen would be identified. In my experience, informed patients will not accept a 5% to 10% chance of receiving a drug that is ineffective if they can be identified up front, particularly given the risks of adverse consequences from tamoxifen and potential for an alternative strategy.

Is testing cost-effective? The CYP2D6 test is commercially available for about \$250. By comparison, a 5-year course of tamoxifen costs roughly \$5,000. Thus, women who would not receive tamoxifen produce a savings for the health care system even after testing for PMs prospectively, to say nothing of avoiding the suffering and salvage maneuvers of administering ineffective therapy upfront. Not least, liability pressures coming from those with relapsed disease in the adjuvant tamoxifen setting are probably indefensible, given the easy availability of CYP2D6 testing already.

The authors did not mention the sulfonotransferase work. This enzyme plays a rate-limiting role in activating 4-hydroxy-tamoxifen, and defective trans-sulfation from SULT1A1*2 homozygosity yields a three-fold increase in death rate,⁴ suggesting another crucial mechanism of tamoxifen resistance. Hopefully commercialization of this test will be accomplished soon to further help in refining clinical decision making.

In the meantime, oncologists should embrace the new insights about tamoxifen and make CYP2D6 testing routine. It is an approach with huge potential benefits for some, and thus represents another incremental improvement in the outcome for breast cancer patients on the whole.

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