

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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CYP2D6 Genotyping and the Pharmacogenetics of Tamoxifen

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H&O Which patients are the best candidates to receive tamoxifen?

DF It is clear that the women who should receive tamoxifen are those with an estrogen receptor–positive tumor that can be confidently demonstrated or those at high risk of developing breast cancer, based, in the United States, on the Gail index. This index, developed by Dr. Mitchell H. Gail, is calculated through a series of parameters arrayed in an equation that predicts risk for breast cancer. High-risk patients may be administered tamoxifen, and this treatment is the standard of care. This drug is very effective in both settings. The breast cancer community gathers every few years in Oxford, United Kingdom, to review the current data in the field. All the trials of tamoxifen are reviewed and the data aggregated by statisticians. The regular updates published as a result of these meetings have shown that the use of tamoxifen for 5 years, as is routine, has a positive effect on the recurrence of breast cancer that lasts at least 15 years after administration ceases. It has recently been shown that when administration ceases, the efficacy remains, but the side effects (eg, hot flashes, aches) notably diminish, as does the risk of deep venous thrombosis. Overall, tamoxifen approximately halves the risk of recurrence of breast cancer.

H&O What is the role of genotyping as it relates to tamoxifen?

DF Genotyping is valuable in settings in which there is a choice of agents and the genetic test can guide the clinician in the decision of which agent to use. Genotyping is not useful in a setting for which only one agent is available.

Because there are alternatives to tamoxifen available in the postmenopausal setting, genotyping may be useful there. Raloxifene (Evista, Eli Lilly) is approved by the US Food and Drug Administration (FDA) for the prevention of breast cancer; for patients who do less well on tamoxifen or for whom tamoxifen is likely to be less effective, raloxifene is a reasonable alternative. In the postmenopausal, adjuvant setting, the aromatase-inhibitor class of drugs is the alternative to tamoxifen. These agents include letrozole (Femara, Novartis), exemestane (Aromasin, Pfizer), and anastrozole (Arimidex, AstraZeneca), which are all approved by the FDA. The aromatase inhibitors appear slightly superior to tamoxifen in terms of efficacy, but have different side-effect profiles.

In high-risk patients, the hypothesis is that those who are congenitally poor metabolizers of tamoxifen and do not produce the active metabolites should receive raloxifene. In the postmenopausal, adjuvant setting, the idea to be tested would be whether patients who are poor metabolizers should receive an aromatase inhibitor. The corollary to this hypothesis is that patients who are extensive metabolizers of tamoxifen might benefit best from tamoxifen rather than aromatase inhibitors. If the poor metabolizers are removed from trial populations, as modeled recently in the *Journal of Clinical Oncology*, tamoxifen may be a better therapy than the alternatives in the prevention and the adjuvant settings. With proper selection of patients via genotyping, it is possible, although not yet proven, that tamoxifen may be more effective than the newer agents available. I believe there is some resistance to this notion based simply on the fact that the community can be biased toward newer therapies because of their novelty.

H&O What does genotyping for tamoxifen entail?

DF The CYP2D6 enzyme has been shown to be responsible for making the active metabolite of tamoxifen. This enzyme has been studied for over 50 years and is well understood outside oncology, but oncologists may be encountering it for the first time as a result of its relationship to tamoxifen. CYP2D6 is completely absent in approximately 7% of the white population. These patients make much less active metabolite of tamoxifen in their systems than those patients in whom the

enzyme is present. The genetic absence of this enzyme in an individual patient results in lower concentrations of active metabolites, and this is the rationale underlying arguments for genotyping.

We, in the Consortium on Breast Cancer Pharmacogenomics (COBRA) do not believe that the data available currently support the use of genotyping in all patients. Nonetheless, there are clinical situations in which it is reasonable to add the results of a genetic test to the dataset a clinician uses, in collaboration with the patient, to decide whether the patient should receive tamoxifen or an aromatase inhibitor in the postmenopausal setting. There is a significant proportion of patients ($\geq 20\%$) who experience toxicities with the aromatase inhibitors and cannot tolerate them. For drugs that are lifesaving to be intolerable to a large number of patients is an important concern for the community. Therefore, it is suggested that these patients undergo the genetic test, which may provide guidance in comparing the risks or benefits of tamoxifen to those of an aromatase inhibitor. The CYP2D6 genetic test is also useful in situations when a clinician is apprehensive about administering an aromatase inhibitor because the patient has vulnerability to a major side effect of the class, most commonly osteoporosis. Small, Asian or elderly, white women who already have had a fracture and then develop breast cancer are good candidates for genotyping because the best methods of preventing osteoporosis do not completely protect against fracture in women receiving aromatase inhibitors. Tamoxifen may be a reasonable alternative in these patients, and knowing the patient's CYP2D6 status will help guide the therapeutic decision-making process.

H&O Is there a role for genotyping in the premenopausal setting?

DF There is no alternative to tamoxifen for the treatment of premenopausal breast cancer; the aromatase inhibitors are ineffective and raloxifene has not been sufficiently studied in this setting. Therefore, genotyping for CYP2D6 is not useful in premenopausal women. It is possible that tamoxifen is less effective in premenopausal women who lack CYP2D6, but because there is no alternative (other than surgical oophorectomy, which may be difficult for many premenopausal women to accept), tamoxifen should still be administered. There are no definitive data on the utility of genetic testing in the premenopausal setting at present, though, so women are counseled not to undergo the test.

H&O What is the need for further research with genotyping in women with breast cancer?

DF Further research in the premenopausal setting will not proceed until an alternative to tamoxifen becomes

available in that setting. In the postmenopausal setting, evidence from eight studies is weighted toward there being an important genetic effect of CYP2D6 on outcomes in patients with breast cancer. However, there are two studies from a Norwegian group that provide data to contradict this assertion. These database studies seem to be well-conducted, and there is no reason to think these data should be discounted. The community needs data from either a small set of randomized prospective trials or a significant number of retrospectively examined prospective trials supporting the use of genotyping in this setting. Data are currently being produced in this regard around the world; trials are ongoing or have recently been completed in Japan, Germany, Norway, and Sweden. The data from Germany, Japan, Korea, Italy, and Hong Kong all lend support to the use of genotyping for CYP2D6 in postmenopausal women. Still, I cannot recommend genotyping all postmenopausal women at this point when the available data would be level of evidence 3 (ie, a single prospective trial retrospectively examined, multiple studies in non-randomized settings, and 2 contradictory studies).

It should be emphasized that it has recently been shown that the women who do not make the active metabolite of tamoxifen tolerate the drug very well. It may be that the women who tolerate tamoxifen best do worst in terms of outcome. They do not experience side effects because their bodies are not producing the active metabolite. In turn, they tend to remain on the drug for a long period of time. The genetic test may also be a predictor of which patients are able to tolerate the drug and thus be compliant. If so, the test would become quite clinically important in this regard. Compliance genetics—predicting which patients can continue to take an agent—is a growing field. For this type of drug (ie, an oral anticancer agent taken for 5 years), for which compliance is critical to the drug's efficacy, this field may become very useful and deserves further investigation.

Suggested Readings

Desta Z, Flockhart DA. Germline pharmacogenetics of tamoxifen response: have we learned enough? *J Clin Oncol*. 2007;25:5147-5149.

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