CLINICAL PHARMACOLOGY

CYP2D6 polymorphisms associated with tamoxifen outcome

For the past 25 years tamoxifen has been the gold standard endocrine treatment for breast cancer. While there is long-term evidence showing that this drug is safe and effective, many women develop resistance to tamoxifen. Most of the effects of tamoxifen are mediated by its metabolites 4-hydroxytamoxifen and endoxifen. The P450 enzyme CYP 2D6 catalyzes the formation of endoxifen from tamoxifen. Many genetic variants of *CYP 2D6* exist that can be broadly categorized into four distinct phenotypes: extensive (normal activity) intermediate (reduced activity), poor (no activity) and ultra rapid (high activity). Some studies have shown a correlation between tamoxifen treatment and poor outcome in patients with poor or intermediate metabolizer genotypes; however, results from other studies produced conflicting results and these studies lacked sufficient statistical power. A large multicenter study published in *JAMA* has now confirmed that there is an association between *CYP 2D6* variation and response to tamoxifen, with better outcomes in patients with two functional *CYP 2D6* alleles (extensive) and worse outcomes in those with nonfunctional (intermediate) or reduced functional (poor) alleles. The authors state, "This study, for the first time to our knowledge, provides sufficiently powered evidence for an association between *CYP2D6* genetics and clinical outcome of tamoxifen".

A total of 1,580 patients were included from a retrospective German cohort and patients from a US cohort from a randomized phase III trial in postmenopausal women were assessed prospectively. Patients had histologically confirmed stage I, II or III primary breast cancer with no evidence of metastases, and had not received previous chemotherapy or endocrine treatment and were hormone-receptor positive.

Patients with extensive metabolism had the lowest probability of recurrence or death, followed by patients with

intermediate metabolism and patients with a poor metabolism had the highest rates of recurrence or death. At 8 years of follow-up, the recurrence rates were 14.9% for extensive metabolizers, 20.9% for intermediate metabolizers and 29.0% for poor metabolizers. Compared with the extensive metabolizers, there was a significantly increased risk of recurrence in intermediate and poor metabolizers, with hazard ratios of 1.4 and 1.9, respectively. Thus, the risk of developing breast cancer was almost 2-fold greater in patients lacking *CYP 2D6* function (poor metabolizers) compared with patients with two functional *CYP 2D6* alleles.

A worse event-free survival and disease-free survival was noted in patients with a decreased *CYP 2D6* activity. No difference in overall survival was observed according to *CYP 2D6* genotype. Stratification for *CYP 2D6* status showed that the time to recurrence data were similar in intermediate metabolism compared to an unselected patient population, whereas in extensive metabolizers the recurrence risk was lower but for poor metabolizers the risk was increased.

In a previous study the researchers showed that *CYP 2D6* variants had no effect on the outcome in a control group of 280 patients who were treated with tamoxifen, a finding that provides strong support that the differences in outcomes seen in women with different *CYP 2D6* genotypes is specific to tamoxifen treatment rather than treatment outcome *per se*. The authors of this study also compared their data with results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) study. They showed that the size of the effect of tamoxifen outcome between poor metabolizers and extensive metabolizers was significantly greater than the hazard ratio differences noted between tamoxifen versus anastrozole in the ATAC study. The researchers comment that, "Our analysis indicates that extensive metabolism patients treated with tamoxifen had an outcome

similar to patients treated with aromatase inhibitors in the ATAC trial and provides new impetus to the medical and scientific community to revisit the issue of relative efficacy of these two approaches in women with early-stage breast cancer." The lead investigator of this trial, Hiltrud Brauch, also commented that, "This study provides robust statistical analysis that will help to open avenues for a genotype guided endocrine treatment for postmenopausal estrogen receptor-positive breast cancer. Our findings provide a powerful argument for refined endocrine treatment." In the future it will be important to establish the precise phenotype (metabolizer capacity) based on each possible genotype by measuring the corresponding tamoxifen metabolite levels.

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Original article Schroth, W. *et al.* Association between *CYP2D6* polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *JAMA* 302, 1429–1436 (2009).