Re: Concordance Between CYP2D6 Genotypes Obtained From Tumor-Derived and Germline DNA

The accuracy of CYP2D6 genotyping and its value for the prediction of tamoxifen outcome are a matter of intense debate (1–11). Technical issues related to genotyping of DNA derived from tumor cores and the resultant unprecedented violation of Hardy-Weinberg equilibrium (HWE) (2) has been at the heart of this debate. Rae et al. (12) published new information comparing CYP2D6 genotypes obtained from various tissue sources. They conclude that “based on less than 10% misclassification rate ... this could not alter the conclusions of the CYP2D6 BIG1-98 investigation” (12).

We applaud Rae and colleagues for obtaining CYP2D6 genotypes within HWE; however, their results and conclusions are irrelevant to our concerns regarding the validity of the BIG 1-98 data (2). That is, Rae et al. did not duplicate the methods of BIG 1-98, where formalin-fixed, paraffin-embedded (FFPE) tumor cores obtained for somatic biomarker studies were used for DNA extraction and CYP2D6 genotypes (obtained after upward of 60 polymerase chain reaction [PCR] cycles (5)) demonstrated massive deviation from HWE (P = 2.5 × 10⁻²). Instead, Rae et al. utilized FFPE cores containing some normal tissue and standard PCR methodology.

In his editorial, Berry compared the North Central Cancer Treatment Group (NCCTG) 89-30-52 (13) and BIG 1-98 data (2) (both used tumor cores), and argues that “since both studies had the same HWE status, the Regan study was resoundingly clear in failing to corroborate the Goetz observation” (14). Berry seems to accept the argument that deletion of the CYP2D6 gene in breast tumor tissue is driving the observed departures from HWE, but inappropriately argues that the genomic constitution of the tumor is the relevant aspect of genome biology to consider, even though it is inherited variation in the germline that alters plasma endoxifen concentrations.

To address NCCTG 89-30-52 HWE issues (13), CYP2D6 genotyping was repeated at Mayo using DNA from FFPE tissue blocks containing nonmalignant tissue as previously published (1) and submitted to the International Tamoxifen Pharmacogenomics Consortium (ITPC) (15). The CYP2D6*4 genotype met HWE (P = .28) and the CYP2D6 genotype was statistically significantly associated with the risk of recurrence, both within NCCTG 89-30-52 and in postmenopausal ITPC patients receiving tamoxifen monotherapy for five years at 20 mg/day (15). To address Berry’s concerns that the ITPC results were “ad hoc,” a secondary analysis in the prospective ABCSG 8 clinical trial (using similar eligibility criteria as ITPC) demonstrated that CYP2D6 genotype was statistically significantly associated with the risk of recurrence or death (8).

Medical practice and the evidence supporting it must pass accepted scientific standards. Data that cannot pass minimal standards for quality cannot be used to test hypotheses critically related to patient care. It is unquestionably true that the oncology community generally focuses on the tumor genome data to classify individuals with respect to their ability to metabolize tamoxifen is inherited variation in the germline that alters plasma endoxifen concentrations.

References


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