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Genetic Polymorphisms of Tamoxifen Biotransformation Predictive of Tamoxifen Pharmacokinetics and its Clinical Implications in Patients with Breast Cancer

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Background: Tamoxifen (TAM) is biotransformed to N-desmethyltamoxifen (NDT) mainly by cytochrome P450 (CYP) 3A, which is further converted to 4-hydroxy-N-desmethyltamoxifen (BX) by CYP2D6. Minor portion of TAM is converted to 4-hydroxytamoxifen (4OHTAM) mainly by CYP2D6. 4OHTAM and BX exert anti-estrogen effect. Pregnane X receptor (PXR) is a key transcriptional regulator of CYP3A and activated by TAM and 4OHTAM. PXR 7635A>G, 8055C>T, -2538C>T are functional variants. Previously, we reported the lower steady state plasma concentrations (SS-conc) of BX and 4OHTAM in patients (pts) with CYP2D6*10/*10, a major variant in Korean (Abstract #634 in ASCO, 2006). To explore the significance of the result, we studied further the association between polymorphisms of genes related to TAM biotransformation (CYP2D6 and PXR) and TAM pharmacokinetics (PK) and made a clinical correlation with outcomes in Korean pts with breast cancer.

Methods: Blood from 202 pts were collected on the median 32 weeks (8-179) of TMX to study the association between the genotypes and PK and additional 33 pts were genotyped without PK. Clinical data were retrospectively reviewed. Plasma TAM, NDT, BX, 4OHTAM were measured by HPLC. CYP2D6*10 were identified by PCR-RFLP and the other CYP2D6 allele was classified as CYP2D6*1. PXR 7635A>G, 8055C>T were determined by single base extension method. This study was approved by IRB at National Cancer Center Hospital and conducted after informed consent.

Results: Of 202 pts, 64 (31.7%) carried CYP2D6*1/*1, 89 (44.1%) *1/*10 and 49 (24.3%) *10/*10. Pts with *10/*10 (n=49) showed lower SS-conc of BX and 4OHTAM than those with the other (n=153) (BX: 7.9 vs. 18.9 ng/ml, $p<0.0001$; 4OHTAM: 1.5 vs. 2.6 ng/ml, $p<0.0001$). However, there was no significant difference in SS-conc of all compounds according to PXR genotypes. Of total 235 pts (202 + 33), 214 were taking TAM in adjuvant setting and 21 in metastatic setting. 42 of 214 adjuvant pts developed disease recurrence with a median follow-up of 41.7 months (4.7-107.3). 15 of them (35.7%) had CYP2D6*10/*10 compared to 38 of 172 pts (22.1%) in remission ($p=0.067$). Of 21 metastatic pts, all 6 nonresponders (100%) in contrast to 6 of 15 pts (40%) who achieved clinical

benefit (CR+PR+SD≥24 weeks) had *10/*10 (p=0.019). CYP2D6 gene was a significant variable associated with TAM response in Cox proportional hazard model (p=0.003) and median time to progression was shorter with *10/*10 (5.0 months, n=12) than the other (21.8 months, n=9) in metastatic pts.

Conclusion: Pts with CYP2D6*10/*10 genotype showed significantly lower SS-conc of BX and 4OHTAM, which could possibly suggest consequent poor clinical outcomes in these pts. Further studies with a larger sample size and longer follow-up are required to verify the result.