Pharmacogenetic/Pharmacogenomic Approaches of Active Tamoxifen Metabolites for Better Individualized Treatment of Breast Cancer

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Tamoxifen is one of the widely used drugs for the treatment of estrogen receptor (ER)-positive breast cancer and its prevention. However, there is a large interindividual variability in its therapeutic or adverse effects. To draw toward optimal tamoxifen therapy is absolutely required for each patient with breast cancer manifesting variable clinical responses. Tamoxifen undergoes extensive metabolism, and the concentrations of tamoxifen and its metabolites vary widely, contributing to the clinical interindividual variability. 4-hydroxy-tamoxifen (4-OH-Tam), though its concentration is much lower than that of tamoxifen, has been considered to play an important role in tamoxifen's anti-cancer effects because of its about 100-fold greater anti-estrogenic potency. Recently, another active tamoxifen metabolite, 4-hydroxy-N-desmethyl-tamoxifen (endoxifen), has been shown to have the identical potency compared with 4-OH-Tam in terms of its ER binding affinity and suppression of estradiol-induced cancer cell proliferation or gene expression. The profiles of global gene expression using the microarray analysis presented highly similar patterns between these two metabolites in breast cancer cells. In addition, steady-state plasma concentrations of endoxifen are 5～10-fold higher than 4-OH-Tam, suggesting that endoxifen could be more important contributor to tamoxifen activity than 4-OH-Tam. Endoxifen is formed predominantly by a highly polymorphic CYP2D6-mediated oxidation of N-desmethyl-tamoxifen, the most abundant metabolite of tamoxifen. Women receiving tamoxifen who either carry genetic variants associated with low or absent CYP2D6 activity or who receive concomitant medications known to inhibit CYP2D6 activity have significantly lower levels of endoxifen. Regarding the effect of polymophisms in tamoxifen metabolizing genes on clinical outcome, it has been recently reported that women with CYP2D6 *4/*4 genotype tend to have higher risk of disease relapse and a lower incidence of hot flashes, suggesting that inter-individual variability in the tamoxifen responses may be partly explained by genetic variation in CYP2D6. This also raise the possibility to improve physicians' ability to select better individualized optimal treatment for each breast cancer patients by predicting the efficacy and toxicity of tamoxifen on the basis of patients' genotypes, medications, and etc. However, more larger prospective tamoxifen trials are awaited for confirmation and the research to unravel the biological complexity also needs to be done to find the gene variants that affect drug response.

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