Impact of UGT2B7 genetics on letrozole metabolism

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The non-steroidal aromatase inhibitor letrozole is used as adjuvant endocrine therapy of postmenopausal breast cancer. Though letrozole therapy has been proven efficient, drug failure with relapse of breast cancer as well as adverse drug reactions such as severe arthralgia have been frequently reported. Currently no data exist whether inter-individual variability of letrozole metabolism may contribute to letrozole drug disposition thereby influencing letrozole response. Whereas the drug metabolizing phase 1 enzymes CYP2A6 and CYP3A4 have already been identified to be involved in the formation of 4,4'-(hydroxymethylene)dibenzonitrile (carbinol), the major metabolite of letrozole, little is known about the UDP-glucuronosyl transferase (UGT) isoforms involved in glucuronidation. We therefore aimed to elucidate (i) the underlying UGT enzymes responsible for the formation of bis(4-cyanophenyl)methyl hexopyranosiduronic acid (carbinol-glucuronide) and (ii) whether genetic variants in UGTs may influence the formation of carbinol-glucuronide.

Phase 2 metabolism via glucuronidation was studied using recombinant UGT isozymes and human liver microsomes (HLM). Enzyme kinetic parameters of letrozole metabolism were determined by incubation of pooled HLM as well as HLM (n=57) genotyped for UGT2B7*2 allele, since the non-synonymous rs7439366 variant (UGT2B7*2) has a frequency distribution of approx. 50% in Caucasians. Genotyping was performed using MALDI-TOF MS (Sequenom). We quantified letrozole and its metabolites, carbinol and carbinol-glucuronide, by the use of a novel established LC-MS/MS method in our lab. In addition to the in vitro experiments, we analyzed steady state plasma levels of letrozole and metabolites in 20 postmenopausal breast cancer patients treated with letrozole (2.5 mg per day).

Based on our in vitro data, UGT2B7 is the only UGT isoform involved in the glucuronidation of carbinol. Incubations using 57 HLM stratified for UGT2B7*2 genotypes (including 19 homozygous variant carriers) did not result in a significant alteration of in vitro glucuronidation activity. Analysis of 20 patients' samples revealed mean plasma levels (± SD) of 366 ± 173 nM, 0.38 ± 0.09 nM, and 34 ± 12 nM for letrozole, carbinol, and carbinol-glucuronide, respectively, indicating remarkable differences in the formation rates of the two metabolic steps. Again, UGT2B7*2 genotypes did not influence letrozole/metabolite plasma levels.

In summary, we firstly described the major contribution of UGT2B7 involved in the formation of carbinol-glucuronide. Moreover, in vitro and preliminary in vivo data suggest no impact of the UGT2B7*2 polymorphism on carbinol glucuronidation. Nevertheless, as glucuronidation of carbinol is highly isoform specific, we suggest carbinol as a novel probe substrate for future pharmacokinetic investigations of UGT2B7.

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