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***In vitro* metabolism of exemestane by hepatic phase I enzymes**

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Abstract

Exemestane (EXE), a steroidal inhibitor of aromatase, dramatically reduces circulating estrogens in postmenopausal women with ER-positive breast cancer. As evidenced by favorable results in the MAP.3 clinical trial on incidence reduction in high-risk postmenopausal women, the potency of EXE in inducing systemic estrogen deprivation and its promising safety profile indicate its further promise as an alternative to tamoxifen in breast cancer chemoprevention. Albeit a commonly prescribed endocrine therapy, little is known about EXE metabolism or the extent to which interindividual genetic variation contributes to differential clinical outcomes. Although its manufacturer states that EXE is predominantly metabolized hepatically by highly polymorphic aldo-keto reductases (AKRs) and cytochrome P450s (CYP450s), neither an exhaustive record of metabolites produced nor the exact enzymes responsible have been disclosed. Multiple human AKRs and CYP450s are known ketosteroids reductases (KSRs), which contribute to phase I metabolism through the transformation of ketosteroids, such as EXE, into hydroxysteroid alcohols, thus, altering their ligand affinities and rendering them substrates for conjugative phase II enzymes. The studies to be presented characterize the *in vitro* metabolic pathway of EXE by hepatic AKR and CYP450 enzymes, as well as identify phase I metabolites produced by cytosolic and microsomal human liver fractions. In particular, the impact of common functional polymorphisms on KSR-mediated EXE metabolite production will be emphasized.