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Impact of CYP2C8*3 on paclitaxel clearance in ovarian cancer patients

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Introduction
Toxicity and therapeutic effects of paclitaxel vary greatly between patients and remain clinically relevant problems with implications on survival and quality of life. Paclitaxel is metabolized to inactive compounds mainly by CYP2C8 in the liver and is a substrate for P-glycoprotein encoded by the ABCB1 gene (MDR-1). We investigated the notion that single nucleotide polymorphisms (SNPs) in CYP2C8 and ABCB1 could be partly responsible for this variation through impact on the elimination.

Hypothesis and Aim
The inter-individual variability in the clearance of paclitaxel is caused by CYP2C8*3 or ABCB1 SNPs: C1236T, G2677T/A or C3435T. The aim of this study was to test the hypothesis in prospectively recruited patients with ovarian cancer treated with paclitaxel+carboplatin.

Results
In 93 patients: the 19 patients carrying the CYP2C8*3 genotype had 11 % lower clearance of unbound paclitaxel than patients without this genetic variant, P-value 0.03. The three ABCB1 SNPs were not significantly associated to the clearance.

Explorative analysis: The 7 patients carrying the CYP2C8*4 genotype had 18 % lower clearance, P-value 0.04.

Conclusion
The genetic variant CYP2C8*3 is associated with approximately 11 % lower clearance of unbound paclitaxel than wild-type patients.

Discussion
An 11 % decrease in clearance is unlikely as sole explanation for the observed inter-individual variability in toxicity and therapeutic effects. The results are nevertheless important because:
1) an impact of CYP2C8*3 has not been demonstrated before in similar studies
2) it fits well with the understanding of how a genotype can impact on a phenotype
3) it adds to the knowledge of factors that contribute to the variability of paclitaxel pharmacokinetics.

References