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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

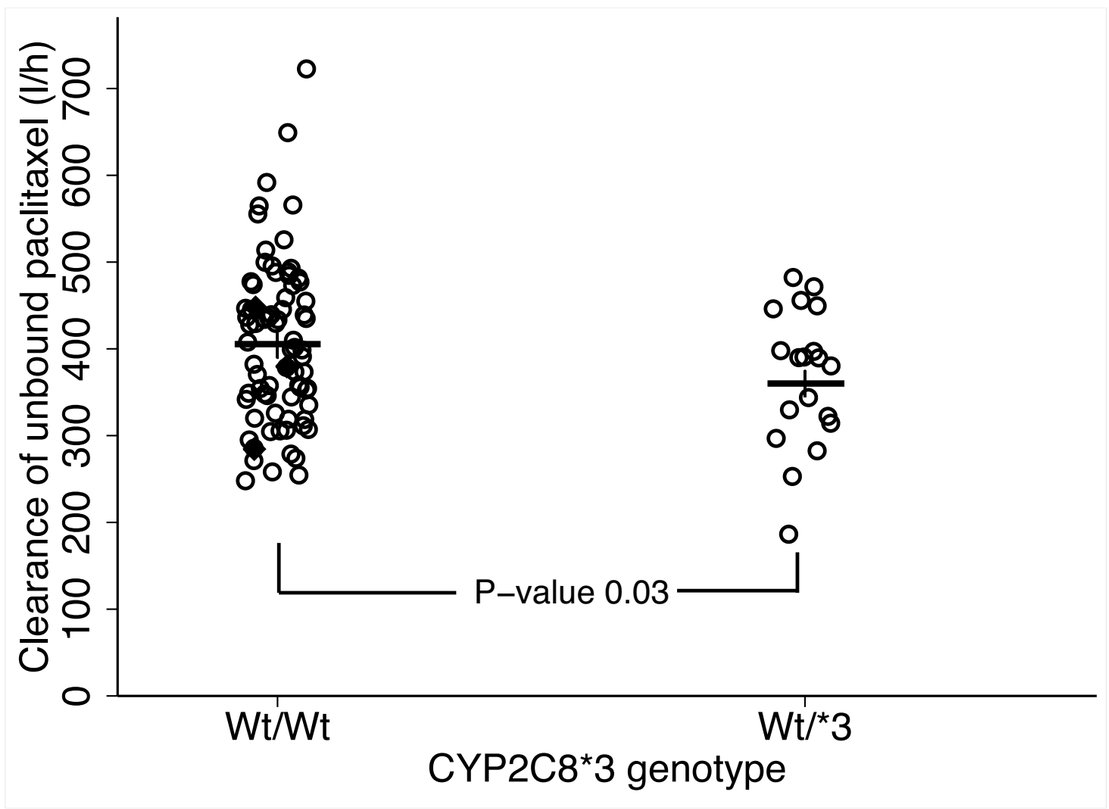
The inter-individual variability in the clearance of paclitaxel is caused by *CYP2C8**3 or *ABCB1* SNPs: C1236T, G2677T/A or C3435T.
The aim of this study was to test the hypothesis in prospectively recruited patients with ovarian cancer treated with paclitaxel+carboplatin.

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.

Clearance as function of *CYP2C83 genotype; N=93**



Black diamonds mark clearance of patients using a CYP3A4 inhibitor.

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 pharmakokinetics.

Methods

Patients: Eligibility criteria included patients with primary ovarian cancer scheduled for therapy with paclitaxel (175mg/m^2)+carboplatin (AUC5-6) every third week. Patients were recruited from four oncology departments in Denmark and one in Sweden from 2007 to 2009.

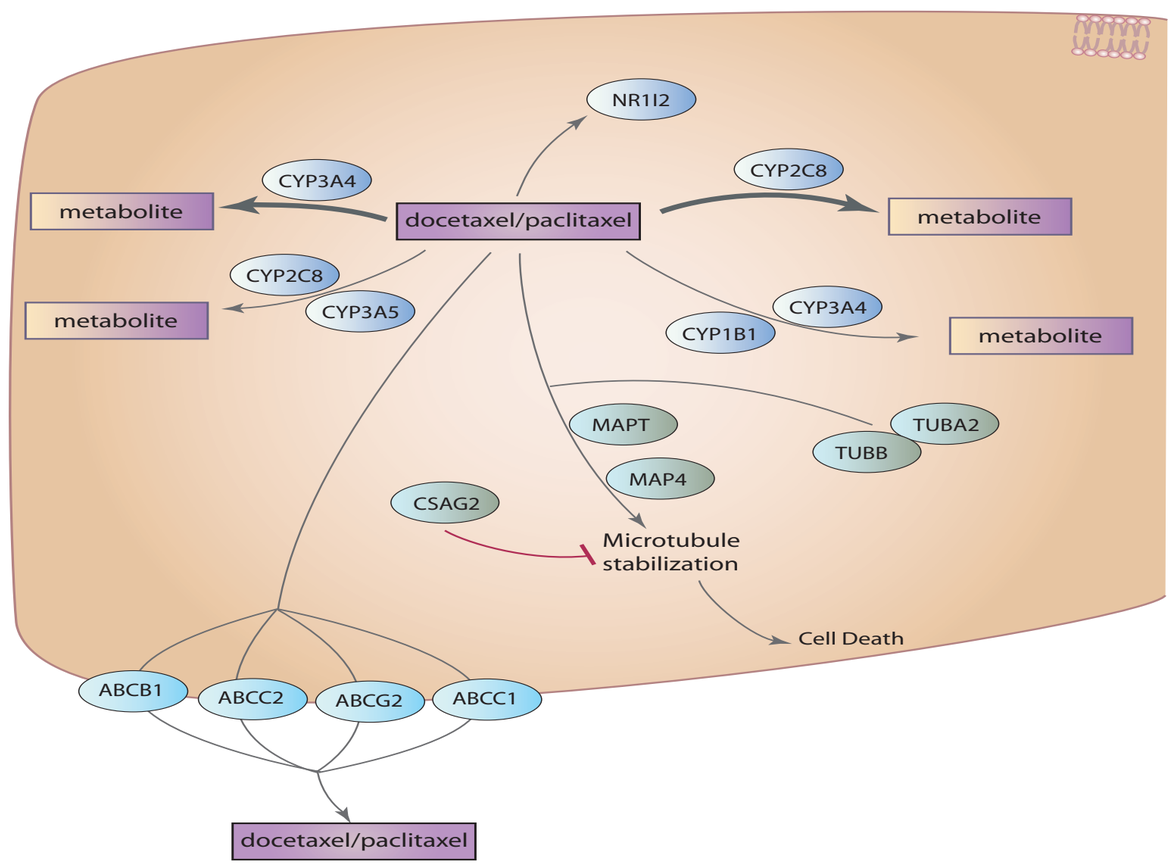
Blood sampling and paclitaxel and Cremophor EL analyses
Three consecutive samples were collected from one cycle from each patient. Sampling times were approximately 3 hours, 5-8 hours and 18-24 hours after start of paclitaxel infusion. The total paclitaxel concentration was determined by HPLC. Cremophor EL was determined using a Coomasie blue assay.

Pharmakokinetic analysis
Empirical Bayes´ estimates of clearance of unbound paclitaxel were achieved from total paclitaxel and cremophor EL concentrations in a non-linear mixed effects analysis carried out using the software NONMEM. A basic two compartment structure was used with constants and covariates from a model described by Henningsson et al(1). The covariates include age, performance status (PS) and body surface area (BSA).

Genotyping was carried out using Pyrosequencing on DNA extracted from whole blood.

Statistical considerations
Log transformed clearance of unbound paclitaxel seemed to be normal distributed (visually assesed). Hypothesis testing was thus carried out using multiple regression (test for trend) with control for age, BSA and PS. Analyses were carried out using STATA10.
In order to address the issue of multiple testing *CYP2C8**3 and the three *ABCB1* SNPs were selected before the statistical analysis was carried out. *CYP2C8**4 and a host of other candidate genes were selected for explorative analysis, for which the P-values should be interpreted with caution.

Taxane pathway. Copyright 2009 PharmGKB reproduced with permission(2).



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