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The Pharmacogenomic importance of Paclitaxel.

by

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Summary

Paclitaxel (Taxol[®]) has a broad activity spectrum and is clinically used, often in combination with carboplatin, to treat breast, ovarian and lung cancer [1]. The response to treatment and the severity of adverse drug reactions after chemotherapy varies greatly among individuals, and one of the most important factors responsible for these differences is now recognized to be the genetic variability. However, so far only genetic variants of ABCB1 have been indicated to be associated with response and pharmacokinetics of paclitaxel. Commercially, the patent on paclitaxel has expired, however, from a health care perspective it would be beneficial to identify patients with risk of poor response or high risk of toxicity to reduce hospitalization costs.

This article will focus on the pharmacogenomic background for paclitaxel response and interindividual variability.

Highlights

- Despite paclitaxel's clinical activity, variability in toxicity, response and pharmacokinetics are high and a major problem.
- It has been indicated that the genetic polymorphism of CYP2C8, CYP3A4 and P-glycoprotein (ABCB1) could affect the response and pharmacokinetics of paclitaxel.
- The gene corresponding to the target protein β-tubulin is highly conserved and genetic variability does not correlate to response.

Context

Predicting the response, the toxicity and pharmacokinetics during treatment with paclitaxel would be highly desirable, in the sense that it would possible to identify patients with high risk of adverse events, patients that would benefit from the treatment and/or patients that might need a higher dose to get a better response. Like most drugs, the effects of paclitaxel are dependent on several proteins. Paclitaxel exert its cytotoxic effect by binding to β-tubulin, thereby stabilizing the microtubule and inducing apoptosis. Systemic elimination of paclitaxel occurs by hepatic metabolism involving the cytochrome P450 (CYP) enzymes, CYP3A4 and CYP2C8 [2]. Paclitaxel is also a substrate for P-glycoprotein, encoded by the ABCB1 (mdr-1) gene, that functions as a transporter and is believed to be an important factor in the resistance to [3, 4] and biliary elimination of [5] many drugs, including paclitaxel. One of the major obstacles to successful treatment is drug resistance. Several potential mechanisms have been suggested for the resistance to paclitaxel, such as mutations in the target protein β-tubulin, single nucleotide polymorphisms (SNPs) in the ABCB1 gene. Another reason might be the high interindividual variability of paclitaxel plasma concentrations, which has been suggested to be influenced by variability in metabolic enzymes and transport proteins e.g. Pglycoprotein.

Mutations in the β -tubulin have indicated as a potential resistance mechanism. However, recent studies have shown that the β -tubulin gene M40 (main isotype) is highly conserved and that mutation in the gene are unlikely to be a clinically relevant explanation of resistance to paclitaxel [6-8].

Different polymorphisms in the ABCB1 gene have been identified and of these SNPs, G1199T/A and the linked G2677T/A (Ala893Ser/Thr) and C3435T (Ile1145Ile, wobble) have

been associated with altered P-glycoprotein expression and phenotype [9-11]. Recently both G1199T/A and G2677T/A were shown to been associated with the progression free survival after paclitaxel treatment [12, 13]. The ABCB1 SNP C3435T has also been associated with paclitaxel-mediated peripheral neuropathy and neutropenia [18]. In another study the progression free survival but not the CA-125 or the clinical/radiological response was indicated to correlate to the G2677T/A [14], although the effects of docetaxel and paclitaxel were not distinguished. However, neither of this was confirmed in a similar study [15]. The AUC of paclitaxel has also been correlated to the ABCB1 genotype, especially the number of variant alleles [16]. However, in other studies no correlation has been found between the pharmacokinetics of paclitaxel and the ABCB1 genotype [17-19]. In the most comprehensive study so far a high interindividual variation in clearance of unbound paclitaxel (10-fold) was found, no statistical significant association was observed between any variant genotype and the pharmacokinetics of paclitaxel [19]. However, a wide range of dosage and infusion times were used in this study.

CYP2C8*3 has been associated with altered turn over of paclitaxel *in vitro* [20-22]. So far CYP2C8*3 has not been associated with either altered pharmacokinetics of paclitaxel *in vivo* [19] or response to paclitaxel treatment [14].

The large interindividual variation in CYP3A4 activity is more difficult to explain on a genetic basis [23], although the CYP3A4*1B seems to affect enzyme activity [24]. For paclitaxel, genetic variations in CYP3A4 might be associated with an altered pathway of paclitaxel metabolism [25] but probably not the total clearance of the drug.

Several other genes have been suggested to affect the response to and pharmacokinetics of paclitaxel. In a breast cancer study CYP1B1*3 was associated with paclitaxel outcome [26], but this was not reproduced in a study of ovarian cancer [14]. SLCO1B3 (gene OATP1B3) has been shown to transport paclitaxel in the hepatocytes, but no association has been found between the pharmacokinetics of paclitaxel and SNPs in the gene [27]. ABCG2 and ABCC2 genetic variants have also suggested to play a role in paclitaxel treatment but no correlations to paclitaxel efficacy has been found [14].

In conclusion, there is an indication that genetic variations in ABCB1 might be associated with response to paclitaxel treatment and altered pharmacokinetics. But the literature is not conclusive on this matter. So far no other genetic variant has been conclusively shown to have an affect on paclitaxel treatment.

Literature

An excellent review on paclitaxel pharmacogenetics has been written by S. Marsh which I would recommend [28]. The largest studies so far on the pharmacogenetics of paclitaxel have been done by Henningsson et al. [19] and Marsh et al. [14], where Hennigsson did not find any association to altered pharmacokinetics of paclitaxel and Marsh did not find any correlation to the response. However, both these studies do have some issues that might have affected the results (see above).

Technology

CA-125 is an indicator for an irritated abdominal cavity both from cancerous and benign causes. It is as a marker for ovarian cancer and for monitoring tumor response during treatment with e.g. paclitaxel. At present there are no diagnostics or markers that have been validated for prediction of paclitaxel ADRs. However, I would anticipate that SNP methodoly, such as pyrosequencing, in the future would be used for identifying individuals of high risk for ADRs and as a tool for personalized medicine.

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Figure

