Pharmacogenetics of taxanes: impact of gene polymorphisms of drug transporters on pharmacokinetics and toxicity

Interindividual variability in drug response and the emergence of adverse drug effects are the main causes of treatment failure in cancer therapy. Functional membrane drug transporters play important roles in altering pharmacokinetic profile, resistance to treatment, toxicity and patient survival. Pharmacogenetic studies of these transporters are expected to provide new approaches for optimizing therapy. Taxanes are approved for the treatment of various cancers. Circulating taxanes are taken up by SLCO1B3 into hepatocytes. The CYP450 enzymes CYP3A4, CYP3A5 and CYP2C8 are responsible for the conversion of taxanes into their metabolites. Ultimately, ABCB1 and ABCC2 will dispose the metabolites into bile canaliculi. Polymorphisms of genes encoding for proteins involved in the transport and clearance of taxanes reduce excretion of the drugs, leading to development of toxicity in patients. This review addresses current knowledge on genetic variations of transporters affecting taxanes pharmacokinetics and toxicity, and provides insights into future direction for personalized medicine.

KEYWORDS: ABC, ATP-binding cassette transporters, paclitaxel pharmacogenetics, SLCO1B3, SNPs, solute carrier organic anion, taxanes, toxicity

The two major clinical taxanes, paclitaxel and docetaxel, are approved for the treatment of breast, lung, ovarian and nonhormone-dependent prostate cancer. Cabazitaxel, which is a modified docetaxel, has been approved for the treatment of hormone-refractory metastatic prostate cancer [1], whereas ortataxel is a third-generation taxane presently undergoing Phase II clinical trials [2]. Paclitaxel was first isolated from the Pacific yew tree, Taxus brevifolia, in 1971 [3]. Presently, the compound is produced through Taxus cell suspension cultures [4]. Docetaxel is a semisynthetic compound derived from 10-deacetylbaccatin III, which is isolated from the European yew tree, Taxus baccata [5]. Chemically, both taxanes are composed of highly oxygenated diterpenes (Figure 1). Taxanes interfere with microtubule dynamics through binding to the β-subunits of tubulin, arresting the cell cycle at the G2/M phase [6,7]. These arrested cells eventually undergo apoptosis [8]. The main challenge in taxane therapy is the high risk of adverse effects, especially peripheral neuropathy and myelosuppression, which usually necessitates dose reduction or changing the treatment regime [9]. Neuropathy could be caused by the aggregation of microtubules in neuronal cells due to the taxane effect on microtubule trafficking [10]. Toxicity of paclitaxel differs greatly among patients and remains a clinically relevant problem with implications on survival and quality of life. Toxicity can result in dose delay, dose reduction or even early cessation of treatment. Significant variability (four- to tenfold) in paclitaxel clearance may contribute to the unpredictability of clinical outcomes [11]. Paclitaxel elimination is regulated by a wide array of genes involved in metabolism and transmembranous transport. The unpredictable interindividual variation in efficacy and toxicity of docetaxel is a major limitation in docetaxel therapy, which can be due to impairment of renal and hepatic function, variability in disease pathogenesis, and severity and drug interactions [12]. Despite the potential importance of these clinical variables in determining drug effects, it is recognized that inherited differences in metabolism and excretion can have an even greater effect on the efficacy and toxicity of drugs [12]. It has been proposed and investigated that SNPs could explain the variability in drug toxicity and efficacy. Sequence variants in the genome might have an impact on clinical outcome either indirectly by altering the drug elimination and/or disposition, or directly by changes in the drug concentration in the microenvironment of the cells in the different tissues.

Membrane drug transporters play a critical role in the disposition of taxanes. ATP-binding cassette (ABC) proteins (i.e., ABCB1 [also known as MDR1; P-gp] and ABCC2 [also...
known as MRP2) [13,14] and solute carrier organic anion transporters (i.e., SLCO1B3) [15] are two such groups of transporters pertinent to taxanes (Figure 2). ABCB1 has important and crucial roles in intestinal absorption and biliary excretion [16,17], whereas ABCC2 and SLCO1B3 have cooperative roles in the docetaxel transport process in the liver [18]. SNPs of genes encoding for these transporters will reduce excretion of the drugs, leading to development of toxicity such as neutropenia, diarrhea and mucositis in patients. Therefore, upon identification and validation of SNPs that are strongly associated with a risk of developing toxicity, pharmacogenetic tests could be performed to determine if patients are suitable for taxanes. This review discusses SNPs of ABCB1, ABCC2 and SLCO1B3 that impact on taxane pharmacokinetics and toxicity.

**ABC**

Drug distribution, metabolism and toxicity is controlled by many factors. Membrane transporters are among the major controllers of drug status in the human body. The ABC transporters are encoded by a large transporter gene family. There have been different ABC transporter genes, based on sequence homology, identified in the human genome, and they are divided into seven subfamilies (from ABCA to ABCG) [19,20]. ATP hydrolysis provides the driving force to transport ABC substrates against the concentration gradient across the membrane. By extruding anticancer drugs from the tumor cells, the chemoresistance of cancer cells was shown to be mediated by a variety of ABC transporters (Figure 2).
transporters [21]. Moreover, ABC transporters are involved in the enterohepatic recycling that affects the biliary excretion. Diseases can induce or inhibit the transporter function by reducing the expression of the transporter (e.g., ABCC2), which is compensated by the enhanced expression of another transporter (e.g., ABCC3 [also known as MRP3]) to limit hepatic toxicity. Based on these facts, new pharmacokinetic models have been established to describe the enterohepatic recirculation (e.g., the sporadic gall bladder emptying model) [22]. However, drug biodistribution is invariably affected by transporter function alteration, which reflects the implications of changes in ABC transporter expression and functionality on pharmacological therapies [23].

Major determinants of chemoresistance in cancer cells were ABCB1 and the ABCC (also known as MRP) family. The main physiological function of ABC transporters is the protection of normal cells and tissues against environmental toxins, which in turn affects the pharmacodynamic properties (efficacy and toxicity) of the anticancer drugs in the human body. The effect of genetic variants in genes encoding transporters might not only affect elimination of the drug via the bile but also likely due to the presence of these transporters on the tissue or on cells such as neutrophils. It has been shown that ABCB1 and breast cancer resistance protein (ABCG2) protect these cells against toxins by the efflux mechanism [24].

**ABCB1**

The ABCB1 is encoded by the *ABCB1* gene [25,26] and is mainly expressed in the liver (Figure 2), intestines, biliary ducts, tumor cells and the

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**Figure 2. Transport, metabolism and elimination of taxanes in the liver.** (1) Uptake of taxanes from the circulation into hepatocytes by SLCO1B3 located in the basolateral surface of the cells. (2) CYP450 enzymes metabolize taxanes into their active and inactive metabolites. (3) Taxanes and their metabolites are excreted into the bile canaliculi by ATP-binding cassette transporters (e.g., ABCB1 and ABCC2). Some polymorphisms of genes encoding for these transporters could result in accumulation of the taxanes in the circulation owing to reduced clearance, which in turn causes toxicity.
endothelial cells of the blood–brain barrier [27,28]. The \textit{ABCB1} G2677T/A polymorphism is responsible for an amino acid substitution (from alanine to serine or threonine). \textit{ABCB1} allelic variants were associated with neuropathy, neutropenia and lower overall survival in combined therapy, while there was no association in the individual docetaxel arm. In addition, there was no association with docetaxel the pharmacokinetics [28]. However, lower \textit{ABCB1} expression [29] and functional changes [30] associated with variant alleles may result in increased toxicity and reduced efficacy of docetaxel [28]. Although there was no alteration in pharmacokinetics of paclitaxel, patients with solid tumors treated with paclitaxel developed neutropenia and peripheral neuropathy, which could be due to inherited variants of \textit{ABCB1} [31]. Neutropenia was significantly associated with the wild-type \textit{ABCB1} G2677T/A polymorphism in a study that investigated different factors influencing docetaxel toxicity and interindividual pharmacokinetic variability in androgen-independent prostate cancer patients [28]. Similarly, a study involving breast cancer patients treated with docetaxel showed a significant association of side effects (fever and febrile neutropenia) with the wild-type \textit{ABCB1} 2677GG (p = 0.024 and 0.027, respectively) [32], whereas there was a significant reduction of nadir hemoglobin in Asian nasopharyngeal carcinoma patients who had \textit{ABCB1} 2677GT and TA genotype treated with docetaxel compared with patients with the GG and TT genotype [33].

The pharmacogenetics of \textit{ABCB1} G2677T/A were investigated in African–American and Caucasian cancer patients. The results did not show significant relationships between \textit{ABCB1} polymorphisms and docetaxel clearance or the docetaxel-related percentage decrease in absolute neutrophil count [34]. However, there was no alteration in the pharmacokinetics of docetaxel with \textit{ABCB1} G2677T/A polymorphisms in patients with solid tumors [35]. A Korean population-based study revealed significant roles of mutant TT, TA and AA genotypes in the \textit{ABCB1} G2677T/A polymorphism as a risk factor for gastrointestinal and hematological toxicities in epithelial ovarian cancer patients treated with taxanes and platinum compounds [36]. A mechanism-based model study revealed a significant association between paclitaxel metabolite (6α-hydroxypaclitaxel) clearance and the \textit{ABCB1} G2677T/A polymorphism. This is explained by a 30% increased clearance in individuals with the GA and GG genotype, while individuals with the mutant TT genotype had a 27% increase in the clearance relative to those with the GT genotype [37]. A similar finding on the significant association of \textit{ABCB1} G2677T/A polymorphisms with paclitaxel and its metabolites’ clearance was reported by Gréen and coworkers, where the clearance of paclitaxel was affected by the G2677T/A polymorphism in \textit{ABCB1}, where the highest clearance was observed in carriers of the GA genotype (26.0 l/h) and the lowest clearance in carriers of the TT homozygous genotype (17.4 l/h) among ovarian cancer patients [38]. Despite showing lower clearance of paclitaxel in subjects with urogenital cancer carrying the TA and TT genotype of the \textit{ABCB1} G2677T/A polymorphism compared with subjects with the GG genotype, the difference in paclitaxel clearance was not statistically significant [39]. The findings were supported by the nonsignificant association that was observed between paclitaxel clearance and \textit{ABCB1} G2677T/A variants in a group of Caucasian women with ovarian cancer who enrolled in a study to investigate the impact of gene polymorphisms on paclitaxel clearance, which has shown no association between paclitaxel pharmacokinetics and toxicity [40]. However, there was no association between the \textit{ABCB1} G2677T/A polymorphism genotypes and paclitaxel clearance in breast cancer patients [41]. Nevertheless, significant associations between the genotype variants of G2677T/A and paclitaxel clinical toxicity, mucositis and diarrhea were observed in patients diagnosed with advanced gastric cancer [42]. A pronounced neutrophil decrease at nadir was observed when primary ovarian cancer patients carrying one or two variants of the \textit{ABCB1} G2677T/A polymorphism were treated with paclitaxel and carboplatin (p = 0.02) [43]. On the contrary, there was no significant association observed between the \textit{ABCB1} G2677T/A polymorphism and hematologic or nonhematologic paclitaxel toxicity in metastatic breast cancer patients [44]. A study by Fransson and coworkers revealed that SNPs causing changes in metabolism or transport had a minimal effect on the plasma concentration of paclitaxel; however, its main metabolite (6α-hydroxypaclitaxel) may be affected by even small changes in the capacity of transport or metabolism [45]. This study proposes that genetic polymorphisms may play an important role for individualizing paclitaxel treatment [45].
When investigating relationships between ABCB1 polymorphisms and docetaxel clearance in African–American and Caucasian cancer patients, the results did not show a significant association between ABCB1 C3435T and docetaxel-related percentage decrease in absolute neutrophil count or with docetaxel clearance. The ABCB1 C3435T polymorphism is responsible for the wobble effect on the glutamic acid [32]. Another study involving breast cancer patients treated with docetaxel showed a significant association between the ABCB1 3435CC genotype and leukopenia [32]. Grade 3 neutropenia was observed in ABCB1 3435TT genotype carriers (p = 0.04) during a pharmacokinetic analysis of docetaxel; however, the study failed to show evidence of an influence of ABCB1 on the pharmacokinetics of docetaxel [46]. A significantly higher risk of neutropenia associated with the presence of the ABCB1 3435TT genotype was reported in operable lymph node-positive breast cancer patients receiving docetaxel containing adjuvant chemotherapy [47]. There was a significant association between the presence of one or two variant alleles of ABCB1 C3435T and neutrophil decrease at nadir (p = 0.03) in patients receiving the paclitaxel and carboplatin regimen for primary ovarian cancer treatment [43].

However, there was clear association of mucositis and diarrhea in gastric cancer patients with CT and TT genotype variants of the ABCB1 C3435T polymorphism [42]. On the other hand, there was no alteration in the pharmacokinetics of docetaxel with C3435T polymorphisms in the ABCB1 gene [35]. However, the association of nadir hemoglobin in relation to the ABCB1 3435CT genotype compared with the CC and TT genotypes was found not to be significant in nasopharyngeal carcinoma patients treated with docetaxel [33]. Nevertheless, the clearance of docetaxel was not affected by the ABCB1 genotype in Asian patients, although C and T alleles of the C3435T SNP of the ABCB1 gene existed in the Asian population [48]. However, there was no significant association observed between the ABCB1 polymorphism C3435T and hematologic or nonhematologic paclitaxel toxicity in metastatic breast cancer patients [44]. Retrospective evaluation of the effects of certain allelic variants in genes encoding enzymes and transporters revealed that there was no statistically significant association between the pharmacokinetic parameters of paclitaxel and the ABCB1 C3435T variant [49], which matches the findings of the study conducted among a group of Caucasian women with ovarian cancer to investigate the impact of ABCB1 C3435T variants on paclitaxel clearance. This study revealed no association of paclitaxel clearance with the studied gene polymorphism [40]. The ABCB1 polymorphisms were among the parameters studied to investigate a possible correlation with taxane pharmacokinetics in a randomized Scottish ovarian cancer trial. This study did not identify any significant candidates for taxane pharmacogenetics and concluded that the validation of potential pharmacogenetic markers is needed [50].

The ABCB1 C1236T polymorphism is responsible for the wobble effect on the glycine amino acid produced. A decreased docetaxel clearance was significantly related to the homozygous mutant C1236T polymorphism in the ABCB1 gene [38]. On the contrary, no significant association was observed between paclitaxel clearance and ABCB1 C1236T and variants in a group of Caucasian women with ovarian cancer who enrolled in a study to investigate the relationship between gene polymorphisms and paclitaxel clearance [40]. Similarly, there was no association between the ABCB1 C1236T genotype and paclitaxel clearance in breast cancer patients [41].

The ABCB1 G1199T polymorphism is responsible for the substitution of the amino acid serine with asparagine. The functional effects of a novel multidrug-resistant ABCB1 variant (G1199T) were evaluated in vitro; paclitaxel was among the panel of cytotoxic ABCB1 substrates selected and recombinant human embryonic kidney cells were used. It was found that ABCB1 G1199A showed increased resistance to certain drugs, including paclitaxel, when compared with ABCB1 wild-type, while ABCB1 G1199T expressed a reduced resistance of 25% of that of ABCB1 wild-type to paclitaxel and other selected drugs (e.g., vincristine, vinblastine and doxorubicin) [51]. Nevertheless, Kimchi-Sarfaty and coworkers found that the cell surface function and distribution of ABCB1 encoded by common ABCB1-coding polymorphisms resemble that of the wild-type ABCB1. Therefore, cell surface expression and functional assays are recommended for the detection of minor differences between ABCB1 polymorphic forms. Moreover, the prediction of transport activity status is more dependent on the haplotype of the transporter than the genotype [52].

ABCB1 SNPs influences toxicity more than the pharmacokinetics of taxanes. Hence, the
association between \(ABCB1\) (G2677T/A and C3435T) polymorphisms and the side effect of taxanes indicates the potential of these SNPs as pharmacogenetic biomarkers.

**ABCC2**

The ABCC2 is mainly expressed in the membrane of bile canaliculi (Figure 2), small intestines, brain endothelial cells and placental trophoblasts. This protein is pharmacologically important in cancer chemotherapy, whereby it plays a critical role in mediating multidrug resistance to diverse classes of anticancer agents [53,54].

The very low oral bioavailability of docetaxel and the interpatient variability in docetaxel exposure were the basis for investigating the role of ABCC2 in the pharmacokinetics of docetaxel in a study that utilized \(Mrp2^{+}\) mice. The results showed an increase in the oral bioavailability of docetaxel by 73% in the \(Cyp3a/Mdr1a/b/Mrp2^{-}\) strain, while only a 10% increase was observed in wild-type mice. This indicates that ABCC2 has a strong impact on docetaxel pharmacokinetics in the absence of CYP3A and Mdr1a/b activity, which affect the metabolism and transport of docetaxel, respectively [55]. Nevertheless, a possible association between \(ABCC2\) polymorphisms (C28548T, A68231G, C101620771G and C101635209T) and grade 3 or 4 leukopenia/neutropenia caused by docetaxel was shown in the Japanese biobank project [56].

A knockout study to investigate the role of \(ABCC2\) and \(ABCB1\) in paclitaxel transport revealed that there was an increase of 1.3-fold in area under the plasma concentration time curve (AUC) of paclitaxel in \(Abcb2^{-}\) mice upon administration of intravenous paclitaxel. The magnitude of increase was found to be exactly the same in the \(Abch1a1/b^{-}\) mice, where \(ABCB1\) dominates the efflux function in the gut and mediates paclitaxel excretion from blood through the intestinal wall into the gut. The absence of both transporters had shown a 1.7-fold increase in the AUC in \(Abcb1a1/b;Abcc2^{-}\) mice. This reflects the individual and combined effect of these transporters on the elimination of paclitaxel [101].

In an in vivo study aimed at assessing the role of \(ABCC2\) in paclitaxel pharmacokinetics in \(Mdr1a1/b/Mrp2^{-}\) mice, it was revealed that the AUC in \(Mrp2^{-}\) mice was higher than in wild-type mice by 1.3-fold. The hepatobiliary excretion of paclitaxel and its metabolites was mainly influenced by \(ABCC2\) and showed a reduction of up to 80% in \(Mrp2^{-}\) mice [57].

The \(ABCC2\) G1249A polymorphism is an important SNP responsible for the substitution of valine amino acid with isoleucine. No significant association was found between \(ABCC2\) polymorphisms (C-24T, A148G and G1249A) and neutropenia, gastrointestinal toxicity or sensory motor neuropathy caused by taxanes in the randomized Scottish ovarian cancer trial [50].

There was a significant association between the less commonly linked polymorphism (\(ABCC2\) T3563A) and paclitaxel-induced myalgia and arthralgia in ovarian cancer patients [58].

\(ABCC2\) polymorphisms as markers of pharmacokinetic changes and side effects of taxanes require further evidence from clinical research to be comparable with other well-established pharmacogenetic markers.

**SLCO1B3**

SLCO1B3 is a solute carrier organic protein encoded by the \(SLCO1B3\) gene and is responsible for docetaxel and paclitaxel uptake from blood into hepatocytes (Figure 2) [59–61]. This protein (also known as OATP1) is an organic anion transporting polypeptide that is expressed in the basolateral membrane of the hepatocyte [62]. The transport of vectorial substrates in \(ABCC2\) and \(SLC21A8\) (a member of solute carrier anions family) double-transfected cells was faster than in single \(ABCC2\)- or \(SLC21A8\)-transfected cells, suggesting that this cooperative transport may be involved in docetaxel transport [18]. This might explain the qualitative or quantitative reduction in docetaxel activity due to functional SNPs, which led to an increase in the docetaxel AUC due to a decrease in hepatic elimination [56]. Nasopharyngeal carcinoma patients with a \(SLCO1B3\) polymorphism of the 5676GG genotype receiving docetaxel had significantly lower clearance of docetaxel and a higher AUC of docetaxel compared with AA and AG genotypes [33]. Although \(SLCO1B3\) was considered as the most powerful influx transporter for docetaxel among the transfected models investigated in a study that aimed to evaluate the affinity and functional significance of docetaxel and variant genes involved in drug disposition, the results of docetaxel clearance in selected patients did not show significant evidence of an association with \(SLCO1B3\) genotypes [63].

Another study supported the conclusion made by Baker and coworkers [6] which involved Spanish cancer patients treated with paclitaxel; it showed no significant association between \(SLCO1B3\) genotypes and paclitaxel-induced...
neurotoxicity [64]. A study on Xenopus laevis oocytes revealed that there was no significant association between SLCO1B3 polymorphisms and pharmacokinetics of paclitaxel [60].

Despite a few studies showing significant associations between SLCO1B3 polymorphisms and toxicity and pharmacokinetics of taxanes, establishing pharmacogenetic markers of taxanes requires more studies involving the combination of the SLCO1B3 polymorphisms with those of efflux transporters, which have a better potential than using efflux or influx transporters polymorphisms individually.

**Conclusion & future perspective**

Taxanes are important drugs in the clinical anticancer armamentarium. Their use in cancer chemotherapy has led to a tremendous improvement in the survival and quality of life of patients with various types of cancers. However, there are subsets of patients that suffer from toxicities related to these drugs, which limit their use. Very often these are associated with genetic polymorphisms of drug disposition systems in the body. One such system is drug transporters. Knowledge of genetic variability and functional polymorphisms in ABC transporters between different ethnic groups are relevant pharmacological factors that can be used to understand variability in drug response. Transporter-gene polymorphisms encoding proteins involved in the transport of taxanes have shown significant correlations with the adverse effects produced by taxanes. Polymorphisms of the ABCB1 gene have shown significant associations with gastrointestinal and hematological disorders as well as neurotoxicity (Table 1). Selection of SNPs as predictors of the pharmacokinetic profiles of drugs is restrained owing to the limited knowledge of the functional significance of genetic variants of ABC membrane transporters. However, the number of studies showing associations, especially of ABCB1 variants, to toxicity and efficacy necessitates further investigation of the role of these transporters in drug bioavailability, metabolism and disposition. Clinical studies did not show sufficient evidence of association between the SLCO1B3 polymorphism and taxane toxicity [58]. Polymorphisms in SLCO1B3 were not associated with taxane pharmacokinetics. More recently, studies also suggest that combinations of genotypes may provide a better prediction for docetaxel pharmacokinetics and toxicity [65]. However, epigenetic regulation, physiologic factors, concurrent medications, herbal remedies and environmental factors are also likely to play a large role in the interindividual variability of response to taxanes. Nevertheless, the association between ABCC2 gene polymorphisms and the occurrence of toxicities to taxanes still lacks evidence and demands further investigations in different ethnic backgrounds at the clinical and molecular levels. Studying different populations of diverse ethnic backgrounds provides better understanding and explanation of the role of polymorphisms of genes encoding for transporters in reducing clearance of taxanes other than the occurrence of toxicities due to accumulation of taxanes in the circulation. It should be realized that there are other factors.

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could contribute to the toxicity and efficacy of taxanes, such as interaction of these drugs with quinone estrogen [66,67] and smoking [68]. The transporters-gene polymorphisms are still at the research stage and more studies involving varied populations are mandatory before a more conclusive outcome can be established. We also believe future studies involving a larger pool of patients should be considered when carrying out such studies as most conducted to date are underpowered; mainly owing to a small sample size. However, even with these limitations, association of ABCB1 SNPs (3435C>T and G2677T/A) with neutropenia have the potential to be developed into pharmacogenetics markers of taxane toxicity. This review establishes a solid platform to create interest for future studies that can either prove or refute the association of transporter polymorphisms with well-defined side effects. We speculate that in the not-too-distant future, upon confirmation of transporters’ SNP-associated side effects, US FDA-approved pharmacogenetic tests could be employed in the clinic to select patients that would respond to taxanes with optimal outcome.

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Executive summary

ATP-binding cassette

- There are different ATP-binding cassette (ABC) transporter genes encoding for transporters, based on sequence homology identified in the human genome.
- A variety of ABC transporters mediate the chemoresistance of cancer cells.
- ABC transporters are involved in the enterohepatic recycling, drug biodistribution and elimination.

ABCB1

- ABCB1 is an ABC transporter encoded by the ABCB1 (also known as MDR1) gene.
- The ABCB1 G2677T/A polymorphism is significantly associated with taxane side effects, mainly fever and febrile neutropenia.
- The ABCB1 C3435T polymorphism is significantly associated with neutropenia in patients treated with taxanes.
- Little evidence has shown an association between the ABCB1 polymorphism and changes in pharmacokinetic profile, particularly clearance of taxanes.

ABCC2

- ABCC2 (also known as MRP2) is a multidrug resistance-associated protein, encoded by the ABCC2 gene, that mediates multidrug resistance to anticancer drugs.
- Association of ABCC2 polymorphism with taxane side effects and clearance has only been shown in in vivo studies. However, clinical studies have shown a possible association of the ABCC2 polymorphism with neutropenia and leukopenia caused by docetaxel treatment.

SLCO1B3

- SLCO1B3 is a solute carrier organic anion transporter responsible for uptake of taxanes from the circulation into the liver.
- Most clinical studies failed to show a significant association between SLCO1B3 polymorphism and pharmacokinetic profile changes of taxanes. Nevertheless, a few clinical and functional SNPs studies have shown a significant association between SLCO1B3 polymorphism and changes in clearance of docetaxel.

References
Papers of special note have been highlighted as:
* of interest
** of considerable interest


7. Tanaka M, Obata T, Sasaki T. Evaluation of antitumour effects of docetaxel (Taxotere®)


** Highlights the impact of inhibiting ABCB1 activity on the pharmacokinetic profile of docetaxel, eliminating the possibility of predicting the physiological and pharmacological effect of the drug based on plasma level alone.


* Discusses the different ABCB1 polymorphisms in association with clinical outcomes in terms of side effects and survival.


* Elaborates the role of gene polymorphisms of enzymes and transporters in the development of different adverse effects of docetaxel.


** Demonstrates a significant effect of a transporter-gene polymorphism (SLCO1B3) on docetaxel clearance.


** Discusses the effect of gene polymorphisms (CYP3A4 and ABCB1) on the pharmacokinetic (clearance) properties of docetaxel.


* Discusses the different ABCB1 polymorphisms in association with clinical outcomes in terms of side effects and survival.


* Explains the interindividual variation in developing side effects (neurotoxicity) due to differences in paclitaxel pharmacokinetics in relation to different enzyme and transporter gene polymorphisms.


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Website

101 UvA-DARE, the institutional repository of the University of Amsterdam (UvA).