Published in final edited form as:

J Oncol Pharm Pract. 2010 March ; 16(1): 39–44. doi:10.1177/1078155209104380.

Clinical Significance of ABCB1 Genotyping in Oncology

Alma Hamidovic, PharmD^{1,2}, Kristine Hahn, PharmD², and Jill Kolesar, PharmD, BCPS, FCCP^{1,2}

¹ University of Wisconsin, School of Pharmacy, Paul P. Carbone Comprehensive Cancer Center

² University of Wisconsin Paul P. Carbone Comprehensive Cancer Center

Abstract

Background—P-glycoprotein (Pgp) is a drug efflux pump that transports natural products, including taxanes and other chemotherapeutic agents, from cells. Several frequent polymorphisms in ATP binding cassette gene B1 (ABCB1) may influence Pgp levels and drug efflux. The purpose of this review was to assess the clinical significance of ABCB1 polymorphisms in oncology.

Methods—Peer-reviewed studies were identified through a search of PubMed/MEDLINE (1990-2008) and the ASCO abstracts (2003-2008) database. Included studies described clinical trials where ABCB1 genotyping was performed in patients with cancer. Search terms included ABCB1, Pgp, docetaxel, paclitaxel, irinotecan, imatinib and anticancer agent. Studies were excluded if the manuscript was not available in English.

Results—The influence of polymorphisms in ABCB1 2677G>T/A, 3435C>T, and 1236C>T and progression-free and overall survival in 309 patients from the Australian Ovarian Cancer Study treated with paclitaxel/carboplatin demonstrated that compared to homozygote GG carriers at 2677, women with the minor T/A alleles were significantly less likely to relapse following treatment. Other trials of ABCB1 genotyping in breast and prostate cancer patients receiving taxanes have shown inconsistent results. Pharmacokinetic studies where ABCB1 was genotyped and patients received irinotecan or imatinib have also shown inconsistent results.

Conclusion—A number of commercially available drugs are substrates for Pgp, and the ABCB1-variant genotypes are frequent and functionally significant, which may have future implications for drug dosing.

Introduction

Inter-individual variations in drug toxicity and efficacy are well-established. While a number of factors may contribute to interindividual variability - including environmental interactions and drug-drug interactions - a patient's genotype¹, is increasingly understood to influence drug disposition and activity and thus may provide a method to individualize drug therapy. Polymorphisms in genes that encode drug metabolizing enzymes, drug targets, and drug transporter proteins are among the most clinically important genotypic variations for many medications. Transport proteins may influence drug disposition by impacting the absorption, distribution, and excretion of many drugs². This is particularly relevant to oncology patients, as many cytotoxic anticancer agents typically have a narrow therapeutic index³.

Corresponding Author: Jill M. Kolesar, PharmD., 600 Highland Avenue Rm K4/554, Madison, WI 53792, Phone: 608 262-5549, Fax: 608 265-8133, jmkolesar@pharmacy.wisc.edu.

At the time this article was written Alma Hamidovic and Kris Hahn were fellows at the University of Wisconsin Comprehensive Cancer Center. Dr. Hamidovic is currently at Abbott Laboratories and Dr. Hahn is at Percitus Biosciences

An extensively-studied and clinically significant transport protein is P-glycoprotein (Pgp). Pgp is a plasma membrane protein encoded for by the ATP binding cassette gene B1 (ABCB1), also known as the multi-drug resistance gene (MDR1)³⁻⁵. Pgp is expressed in normal tissues in the on the peripheral blood mononuclear cells, including natural killer cells, CD8+, and CD4 + cells, small and large intestines, kidneys, liver, brain as part of the blood-brain barrier, testis, muscle, placenta, and adrenals,^{6,7} and its physiologic function is to protect cells from xenobiotics by functioning as an efflux pump.

Pgp also has the potential to limit the oral absorption of xenobiotics, by pumping them back into the intestinal lumen. In general, the drug needs to be large in size (> 800 Da), poorly water soluble, and slowly absorbed for Pgp to significantly reduce its intestinal absorption. For rapidly absorbed drugs, Pgp may become saturated and unable to efflux drugs and xenobiotics efficiently⁸. Therefore the influence of Pgp on oral absorption is dependent on the characteristics of the drug. At the tissue level, where drug concentration are lower, Pgp does not become saturated and generally reduces the tissue concentrations of substrate compounds.

Polymorphisms in ABCB1 may influence Pgp substrate specificity, and ultimately drug pharmacokinetics, efficacy and toxicity. C1235T, G2677T/A, and C3435T are functionally significant and common⁹. For example, the homozygous CC genotype in exon 26 (C3435T) is associated with a two-fold higher Pgp protein expression levels compared with the TT genotype^{8,10,11}. For this reason, individuals with the CC genotype would be expected to have two-fold higher drug efflux which would result in lower oral bioavailability and lower tissue concentrations. This suggests that ABCB1 genotyping may be important for individualized drug treatment.

With advances in genotyping technology, such as pyrosequencing, which is described in the section on genotyping methods, and an increased understanding of the clinical significance of Pgp polymorphisms, genetic polymorphisms may soon be assessed as part of routine clinical management for patients receiving treatment for cancer. The purpose of this paper is to evaluate the clinical significance of ABCB1 polymorphisms in oncology.

P-Glycoprotein Structure and Function

Pgp is a plasma membrane protein that exports substrates via ATP hydrolysis and is essential in protecting the cell from cytotoxic drugs and natural compounds¹². The efflux pump is comprised of a 170-kDa transmembrane protein that is N-glycosylated on the first extracellular loop.¹² There are two hydrophobic transmembrane domains that dimerize and form a pore. This pore is important in transporting solutes through the membrane and thus contributes to substrate specificity. Substrate binding occurs on the cytoplasmic surface¹². Polymorphisms leading to changes in the amino acids at the cytoplasmic surface may alter substrate specificity¹¹. A broad range of hydrophobic cytotoxic and noncytotoxic drugs are substrates of Pgp (Table 1). Normally, Pgp functions to transport toxic substances out of cells and to protect the cells and organs from toxic injury⁹. Tumor cells that overexpress Pgp may be resistant to anticancer agents because of altered pharmacokinetics and reduced intracellular concentrations of anticancer agents⁹. Clinical trials with MDR-reversal agents have suggested that inhibiting Pgp with noncytotoxic compounds may overcome resistance; however, these trials have generally been limited by toxicity¹³.

Genetic Polymorphisms of ABCB1

ABCB1 is located on chromosome 7q21.1 and consists of 28 introns and 28 exons^{6,14-16}. ABCB1 mRNA is 4.7 kb and is contained in a coding region of 120kb^{6,17}. The ABCB1 gene has been extensively studied for its characteristic polymorphisms, with at least 50 SNPs identified for ABCB1¹⁸. Three polymorphisms frequently studied for their effects on Pgp

expression, functionality, and substrate distribution are C1236T, G2677T/A, and C3435T^{10, 11}. These genes are located on exons 12, 21, and 26 of the ABCB1 gene, respectively¹¹. The SNPs represent the three most frequent ABCB1 SNPs in the Caucasian population and have been shown to be in linkage disequilibrium¹⁹. G2677T/A is at a wobble position which results in an Ala to Ser/Thr change at position 893²⁰. C1236T is a synonymous mutation resulting in a Ser to Asn change at position 400²¹. C3435T is also a synonymous mutation at a wobble position but does not change the amino acid from an Ile at position 1145²². The allelic frequencies of these three SNPs are highly variable between ethnicities^{11, 19, 22} (Table 2).

Clinical Implications of the ABCB1 Genotype

Paclitaxel and Docetaxel

Both paclitaxel and docetaxel are routinely used in the treatment of breast, ovarian and lung cancer and are substrates of Pgp. The influence of Pgp SNPs on patient outcome has been most comprehensively studied in ovarian cancer, where Marsh and colleagues assessed 27 polymorphisms from 16 genes involved in taxane and platinum pathways in 914 patients from the SCOTROC1 phase III trial²³. Patients in this trial were randomized to receive carboplatin with either docetaxel or paclitaxel (see Table 3). No significant association was found with ABCB1 2677G>T/A genotype and clinical or radiological response, toxicity or progression free survival ($P = 0.66$, $p > 0.05$ for all toxicities, and $p = 0.862$ respectively).

Johnatty and colleagues²⁴ recently evaluated the correlation between ABCB1 2677G>T/A, 3435C>T, and 1236C>T polymorphisms and progression-free and overall survival in 309 patients from the Australian Ovarian Cancer Study who were treated with paclitaxel/carboplatin. Compared to homozygote GG carriers at 2677, women with the minor T/A alleles were significantly less likely to relapse after treatment ($P = 0.01$). A sub-group analysis for those who received optimal de-bulking (less than 1cm minimal residual disease) also demonstrated a significant association between 2677G>T/A genotype and disease progression, with a 49% risk reduction in disease progression for heterozygote and homozygote carriers of the minor 2677T/A allele compared with GG homozygotes in the optimally debulked group (PLog-rank = 0.0004) but not for patients with suboptimal debulking (PLog-rank > 0.3). The SCOTROC1 trial was then used as an independent validation set for the data in this study. A comparison showed a similar relationship between the bulk of residual disease and the 2677G>T/A genotype. Patients with no or microscopic residual disease who were treated with either paclitaxel or docetaxel and who expressed a 2677T/A allele had improved progression-free survival when compared to those who did not express the 2677T/A allele (unadjusted HRT/A carriers, 0.70; 95% CI, 0.46-1.04; P one-sided = 0.039; stage-adjusted HRT/A carriers, 0.62; 95% CI, 0.37-1.03; P (one-sided) = 0.033).

The mechanism for these differences in function remains unclear. While the 2677G>T/A SNP results in an amino acid change from alanine to serine or threonine, the effect of the amino acid change on Pgp protein level has not been demonstrated³. The most likely mechanism may be a pharmacokinetic mechanism. As demonstrated by Wong and colleagues²⁶ patients with the GG genotype had increased clearance, resulting in decreased drug exposure and a potentially poorer outcome when compared to those with the T/A variant.

Several smaller studies of paclitaxel in various tumor types provide conflicting results²⁶⁻²⁸ (See Table 3); however, these are likely limited to small sample size. In addition, the effect of the 2677 T/A SNP may be affected by different dosages of chemotherapy administered as saturation of Pgp may not occur at lower drug concentrations, concurrent medications which may also interact with Pgp, different assay methods for ABCB1 genotype and tumor types, which may or may not overexpress Pgp. In the absence of prospective confirmatory studies, it

appears that carrying the 2677 T/A alleles may improve progression free survival and response in women with ovarian cancer receiving a taxane.

Irinotecan

Irinotecan is a topoisomerase I inhibitor that is used commonly to treat colon and lung cancer. It is also a substrate for Pgp²⁹. Several studies have been conducted to evaluate the influence of ABCB1 polymorphisms on irinotecan pharmacokinetics²⁹⁻³¹. In a small trial, irinotecan was administered to 65 cancer patients, and pharmacokinetics and genotyping were performed. This trial demonstrated the homozygous T allele of the ABCB1 1236C > T polymorphism was associated with significantly increased exposure to irinotecan ($P = 0.038$) and its active metabolite, SN-38 ($P = 0.031$)²⁹. In a study of Japanese colorectal cancer patients, an ABCB1 haplotype 1236T, 2677T and 3435T was associated with reduced renal clearance of irinotecan and its metabolites³⁰. In contrast, in a study of 107 NSCLC patients treated with irinotecan and cisplatin, 2677TT/3435TT carriers showed a significantly lower plasma AUC of SN-38G ($P = .006$), when compared 2677GG/3435CC carriers³¹. In general, those with the variant allele, and presumably less efflux, have increased plasma exposure to irinotecan and SN-38, although an association with increased toxicity or outcome has not been described. This may be related to the complex metabolic pathway of irinotecan, where ABCB1 makes a relatively small contribution.

Imatinib

Imatinib is an oral anti-cancer agent used for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST), and is also a substrate for Pgp³². In a study of imatinib pharmacokinetics, oral clearance (CL/F) values for ABCB1 1236T>C, 2677G>T/A, and 3435C>T genotypes were compared on day one of therapy and at steady-state³³. While there was no association between estimated day 1 imatinib CL/F and the ABCB1 (MDR1) SNPs, a significant association was observed at steady state. Patients with homozygous T nucleotide at each of the 1236T>C, 2677G>T/A, and 3435C>T loci had higher estimated imatinib CL/F than those with the wild-type CC or GG genotype, while results for heterozygotes were intermediate. Homozygous TT genotypes would be expected to express less Pgp, efflux less drug, have higher plasma levels, as less drug is being eliminated. Therefore, these results are generally consistent with those reported in the ovarian studies, where variants had improved outcomes.

Genotyping Methods

ABCB1 genotyping, while potentially clinically relevant, is not routinely performed. This may be due, in part, to the lack of validated assay methodology for ABCB1 SNP evaluation. In addition, different genotyping methods used across studies may contribute to the difficulty in interpreting results.

We have validated a genotyping method utilizing pyrosequencing for the three common ABCB1 polymorphisms, C1236T, G2677T/A, and C3435T³⁴. This assay was validated via intra- and inter-assay variation determination and by comparison to direct sequencing, the accepted standard for genotyping assays. Pyrosequencing results were 100% reproducible as each assay repeatedly produced the expected genotype call. As there was no disagreement, the relative coefficient of variation was 0, denoting no variation. To confirm the accuracy of genotype scoring by pyrosequencing, direct sequencing was carried out. The results were unambiguous, and the concordance for both directions of C1236T and C3435T, and reverse G2677T/A with the pyrosequencing call was 100%. Consequently, the calculated overall kappa coefficient was 1, denoting perfect agreement that is well above that expected by chance alone.

Conclusion

A number of commercially available drugs are substrates for Pgp, and the ABCB1 variant genotypes are frequent and functionally significant. The best evidence for a clinically significant role for ABCB1 is currently in women with ovarian cancer receiving a taxane who carry the 2677 T/A allele, which improves progression free survival and response, potentially through a pharmacokinetic mechanism. Many ABCB1 genotyping studies demonstrate conflicting results, potentially due to different disease being assessed, different drug combinations, different pharmacokinetic endpoints (Area under the curve vs Clearance), and different genotyping methods. Pyrosequencing is equivalent to direct sequencing in accuracy and is an acceptable method for genotyping.

Acknowledgments

U01CA062491 “Early Clinical Trials of Anti-Cancer Agents with Phase I Emphasis” NCI; CTEP Translational Research Initiative Funding 24XS090, and 1ULRR025011 Clinical and Translational Science Award of the National Center for Research Resources, NIH.

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Table 1
P-Glycoprotein Substrates Clinically Relevant to Oncology

Anti-cancer Agents^{6,9,13-16}	
Actinomycin D	Mithramycin
Bisantrene	Mitomycin C
Colchicine	Mitoxantrone
Daunorubicin	Paclitaxel
Docetaxel	Temozolomide
Doxorubicin	Teniposide
Epirubicin	Topotecan
Etoposide	Vinblastine
Irinotecan	Vincristine
Methotrexate	Vindesine
Examples of MDR-Reversal agents in clinical trials¹⁵	
Verapamil	Tamoxifen
Cyclosporine A	Azidopine
Quinidine	

Table 2

SNP Frequencies in Various Populations

Ethnicity	C1236T Rs:1128503 CC/CT/TT	G2677T/A Rs:2032582 GG/GT/GA/TT/AA	C3435T Rs: 1045642 CC/CT/TT
Asian ²²	13%/46%/41%	21%/60%/18%/1%	31%/51%/18%
European Caucasian ^{11,19}	14%/48%/38%	31%/50%/19%/0%	22%/50%/28%
African American ¹⁹	76%/22%/2%	72%/22%2%/0%	62%/34%/4%
Hispanic ³⁵	28%/50%/22%	31%/53%/16%/0%	30%/49%/21%

Table 3
Clinical Implications of ABCB1 genotype in Patients Receiving Taxanes

Population (n)	Regimen	Polymorphisms Evaluated	Clinical Significance	Ref
Paclitaxel and docetaxel				
Ovarian cancer (309)	Paclitaxel Carboplatin Doses not reported	2677G>T/A 3435C>T 1236C>T	G2677 T/A (variants) with less relapse	24
Ovarian cancer (53)	Paclitaxel Carboplatin	G2677T/A C3435T	G2677T/A (variants) more likely to respond treatment	27
Ovarian cancer (1077)	Docetaxel carboplatin or paclitaxel carboplatin	<i>ABCB1</i> 1236C>T, 2677 G>T/A, and 3435 C>T	No effect	23
Breast cancer (108)	Paclitaxel 175mg/m² q 3 weeks	2677G>T/A 3435C>T	3435 CT genotype associated with poorer response and decreased OS when compared to CC genotype (wild-type)	26
Prostate cancer (73)	Docetaxel or Docetaxel + Thalidomide	<i>ABCB1</i> 1236C>T, 2677 G>T/A, and 3435 C>T	1236 CC (wild-type) with improved survival 2677 GG (wild-type) with improved survival	28