Pharmacogenomics of Drug Transporters: A Comprehensive Review

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ABSTRACT: ***Pharmacogenomics attempts to explore people who are susceptible to toxicity and poor response to conventional anticancer medication dosages. The therapeutic relevance of pharmacogenomics research that has already been done is still a hot subject. Though protein pharmacogenomics is well-studied in stage 1, the clinical consequences of stage II genetic diversity in enzymes or drug transporters are less well understood. The effect of pharmacokinetics, particularly the danger of some clinically variable medicinal medicines, on membrane transporters has grown in the last ten years. Polymorphisms can have diverse, sometimes even conflicting, pharmacokinetic and pharmacodynamics consequences in various cancers in response to various medicines, according to studies of different regimens and tumour types. More thorough knowledge on the various polymorphisms in drug-metabolizing enzymes and drug transporters is required for the practical use of pharmacogenomics in cancer treatment. Before personalized therapy may be used on a regular basis, a better knowledge of the intricacies of pharmacogenomics is required. This paper provides an overview on pharmacogenomics of drug transporters.***

KEYWORDS: ***Anticancer, ABC, ATP-Binding, Drug Transporters, Pharmacogenomics.***

1. INTRODUCTION

The study of the hereditary basis of inter individual variations in medication response is known as pharmacogenomics. One method is to look for genetic variations linked to severe side effects, which may then be used to screen for those who shouldn't take the medicine or should take it at a lower dose. Another strategy is to look for biomarkers that can predict medication effectiveness. Evaluating medication response variability appears to be especially important in cancer, where the stakes are high, medicines often have a limited therapeutic index, and toxicities could be severe. Before starting cancer chemotherapy, pharmacogenomics screening might help identify individuals who are at a higher risk of toxicity or have a lower chance of responding. Pharmacogenomics has the potential to lead to customized medication therapy, often known as individualized medicine[1].

1.1. Drug transporters:

ATP-binding cassette conveyors and solvent conveyors are also the two widely researched membrane conveyors. So far, almost 400 distinct proteins have been identified in these two categories. Based on the delivery method and its function in cellular absorption and efflux, the broad distribution of both endogenous chemicals and xenobiotics throughout the body is thought to be a major variable in the pharmacokinetics of commonly used medicines as shown in Figure 1.

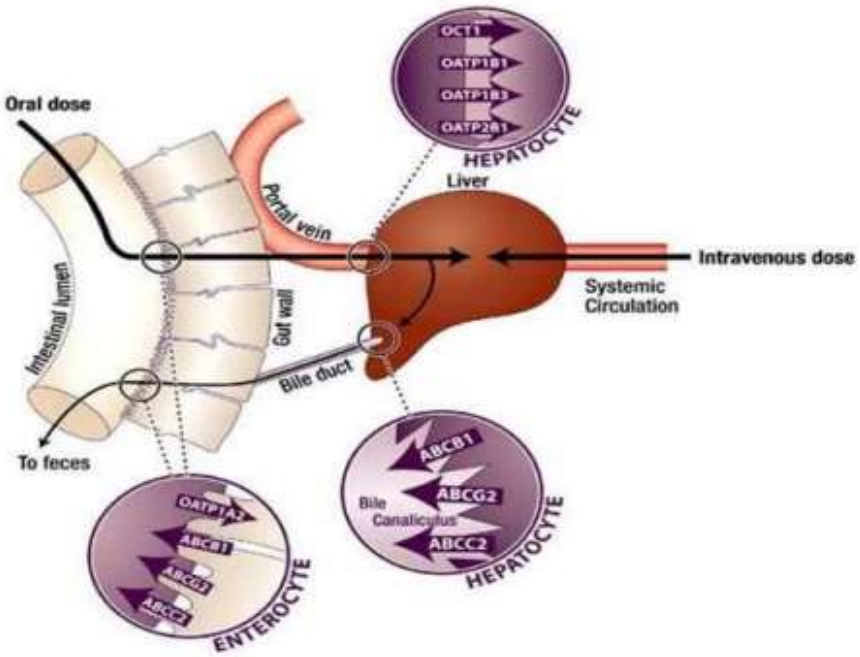

Figure 1: Schematic diagram showing localization of ABC AND SLC transporters involved pharmacokinetics, especially oral absorption from the GI tract.

1.1.1. Breast cancer resistance protein:

BCRP (or ABCG2) appears to play a function in tissue protection by actively moving harmful chemicals and xenobiotics from out cells. Anticancer medicines based on mitoxantrone, methotrexate, doxorubicin, and camptothecin, including such topotecan and SN-38, demonstrate multidrug resistance with cancer cells overexpressing ABCG2. Oral availability or clearance of medicines that are ABCG2 substrates, particularly topotecan, have shown large inter individual variations[2].

The impact of the polymorphisms G34A and C8825A, which result in a V12M and Q141K amino acid substitution, correspondingly, on the transporter structure of the protein, was investigated. Drug resistance to indolocarbazole, a topoisomerase I inhibitor, would be less than 1/10 in cells expressing V12M or Q141K compared to the wild ABCG2-transfected cells, as well as the variant ABCG2-expressing cells had enhanced drug accumulation and decreased drug efflux. The fact that now the ABCG2 transporter is not localized to the apical membrane in the V12M clone might explain this changed function of the ABCG2 enzyme[3].

1.1.2. P-glycoprotein:

Several SNPs in the ABCB1 gene are associated, and genetic variants in the P-gp gene may be relevant in affecting the result of pharmacotherapy. The 3 SNPs that have been discussed the most of these are given below.

- *6 (C3435T)
- *7 (G2677T/A), and
- *8 (C1236T)

A frequent haplotype (P-gp*2) was discovered to include three SNPs at the same time: *6, *7, and *8, with a frequency of 60% among European Americans. Direct sequencing of DNA from patients who were homozygous for all three SNPs strongly showed that they would be connected to polymorphic locations at regulatory regions of the P-gp promoter, which might explain the differences in regulatory kinetics[4].

P-gp polymorphisms have also been linked to treatment outcomes in AML patients. Patients homozygous for both the wild-type allele at a certain locus studied (exons 12, 21, and 26, respectively, for P-gp*8, *7, and *6) had a considerably worse overall survival and a greater chance of relapse when treated only with anticancer medicines etoposide, mitoxantrone, or daunorubicin. Reduced intracellular concentrations of anticancer medicines due to P-gp activity in AML blasts might theoretically be linked to AML therapy failure and disease resistance. Individuals with homozygous mutations for *6 and *7 have been at the greatest risk of developing

medication resistance during lymphoproliferative illness therapy. Another research found that individuals with the homozygous mutant *6 genotype had a different reception to preoperative treatment in breast cancer patients.

1.1.3. Models for Studying the Role of P-Glycoprotein:

The mdr1a-/- rat is among the most efficient models for studying the role of intestinal P-gp in vivo. The abundant P-gp mostly in blood-brain barrier pumps ivermectin out of another brain in normal animals, but in mdr1a-/- rats this is absent, leading to approximately 100 times the buildup of ivermectin in the brain. P-gp also inhibits numerous major brain medications such as vinblastin, dexamethassone, digoxin, cyclosporin A, ondansetron, and loperamide form accumulating inside the barrier function[5].

P-gp and CYP3A have been investigated in terms of peptide and peptidomimetic intestinal permeability, and the influence of CYP3A and P-gp on total bioavailability has been shown to be considerable. Most of the accessibility of these drugs should rise if either or several of these systems is blocked and the variation in the estimated dosages of the systemic drugs should be reduced.

1.1.4. Polymorphism of P-gp:

Only seldom in the study have P-gp polymorphism been recorded, with most findings originating from P-gp mutation in cells. The bulk of data were derived from PGP mutating artificially applying molecular biology or employing culture cells as medium for selection. The CF-1 sub-population contains naturally expressed faulty P-gp, which makes them more susceptible to substance neurotoxicity and creates a risk of chemical birth defects[6].

1.2.Effect of polymorphisms in genes encoding drug transporters:

A drug may be beneficial or detrimental to a certain patient. The drug's absorption, distribution, and excretion rates have a significant impact on the kind and breadth of the resulting impact. Drug transporters are all in charge of allowing all medications, as well as its inactive and active metabolites, to enter and leave cells. As a consequence, mutations in the drug transporter gene can influence medication absorption, distribution, and excretion rates, and also the safety and efficacy of the medications administered[7].

- *ABCG2:*

ABCG2, also referred to as the breast cancer resistance protein (BCRP), mitoxantrone resistance protein (MXR), or placenta-specific ABC protein, was identified in multidrug-resistant cell lines, comparable to ABCC1 (ABCP). ABCG2, which is found in epithelial cells of the small intestine, lung, kidney, sweat glands, colon, and placenta, is required for drug absorption and biliary excretion. The ABCG2 gene has been shown to contain over 80 polymorphisms. SNP C421A in the variation, for example, has been linked to decreased expression and changed substrate specificity. ABCG2.

- *ABCC1 and ABCC2:*

Particularly ABCC1 and ABCC2, as significant ABC members, play a role in the transport and excretion of a variety of chemotherapeutic drugs, toxicants, and organic anion compounds. Glutathione cotransporter is required for the transport of certain substrates, such as estrone sulphate, by both transporters. Significant correlations between the G671V variation and a V188E-C1515Y haplotype of ABCC2 and G671V variant with 28 percent allelic frequency in Caucasians have been found in non-Hodgkin lymphoma treated patients using doxorubicin.

- *ABCB1:*

P-glycoprotein (Pgp) which would be involved mostly in cellular efflux of various chemotherapeutic drugs, physiological metabolites, and carcinogens, is encoded by the ABCB1 gene, widely referred as multidrug resistance 1. ABCB1 is highly polymorphic, with various populations having varying rates of allelic variations. Polymorphisms in ABCB1 in several cancer cell lines in 1988 and afterwards. Patients with this haplotype had normal transporter characteristics, however their transporter inhibition by tiny modulators was compromised. The contradictory findings of these investigations might be due to unidentified polymorphisms other than the investigated mutations, or they could represent the substrate medicines' complicated disposition routes in the individuals. For example, ABCB1 transports cyclosporine, a CYP3A4 substrate that is commonly utilized as an immunosuppressant among patients with liver, kidney, or heart transplants.

- *OCTs:*

OCTs are proteins encoded by the SLC22A family and in humans, which are present in the basolateral cell membrane of the renal proximal tubule three isoforms, OCT1, OCT2, and OCT3, have been identified in humans and OCT2 is highly expressed in the kidneys. OCTs mediate. The cellular uptake of a wide range of structurally-different organic cations including clinically-administered drugs such as metformin and procainamide. Patients with type 1 diabetes who are homozygous for the variant exhibit a significantly higher renal clearance and lower plasma concentration of metformin than those with the homozygous variant. The focus of this article is to examine and explain what is currently known about five key variables that impact drug transporter activity, such as drug transporter expression and function as shown in Figure 2.

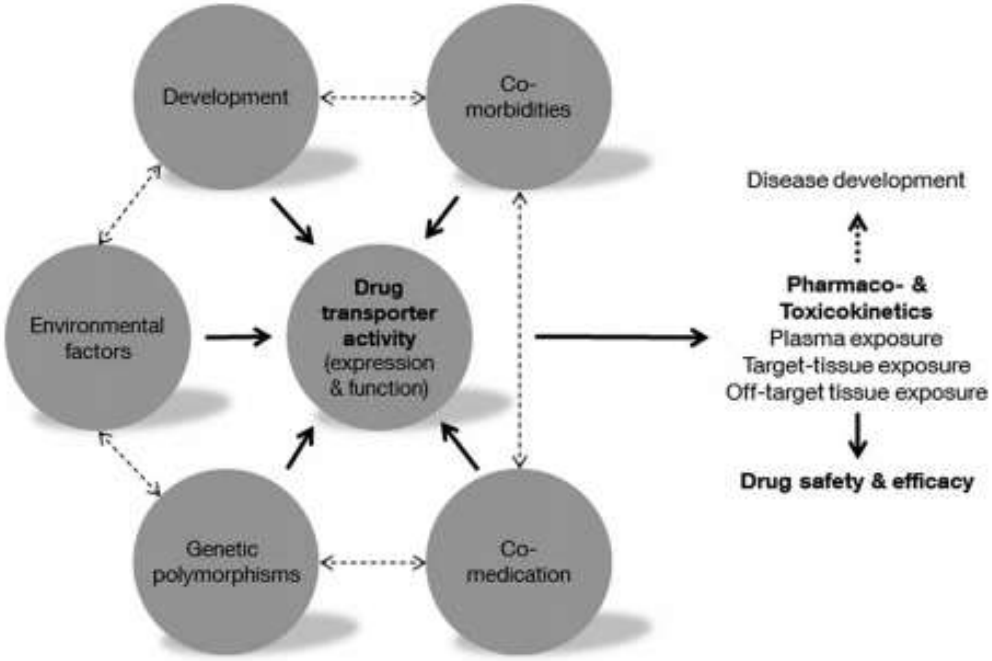

Figure 2: Factors that influence drug transporter activity including transporter-dependent pharmaco- and toxicokinetics in children, possibly affecting medication safety and effectiveness as well as illness progression.

2. LITERATURE REVIEW

Vincent H.L. Lee studied the third millennium began with a huge victory that will have a significant influence on the quality of living in our time. Disease prevention, customized treatment, and genotype-based medicine will all be a reality in the not-too-distant future. It took nearly two decades for scientists to figure out that cytochrome p450 2D6 was in charge of drug metabolism. This scientific breakthrough brought attention to the role of gene expression in medication response. The rising acceptance/awareness about drug transporters as a doorway to epithelial drug transport is just a parallel trend in drug delivery which might also benefit first from Human Genome Project's fruits. This discussion highlights an important topic: the potential influence of drug transporter genetic variation on pharmacokinetics and the challenges it offers in drug delivery[8].

Rafid Salim Jabir et al. studied the primary causes of therapeutic failure in cancer therapy are inter-person heterogeneity in medication response and the development of undesirable pharmacological effects. Drug transporters in the membrane have an essential role in pharmacokinetics, treatment resistance, toxicity, and patient survival. Pharmacogenetics investigations of these transporters are likely to lead to novel therapeutic methods. Taxanes have been authorized to treat a variety of malignancies. SLCO1B3 absorbs circulating taxanes and transports them to hepatocytes. Polymorphisms in genes that code for proteins involved in the removal and clearance of taxanes decrease drug excretion, resulting in toxicity in sufferers. This review highlights existing information about genetic variants in transporters that impact taxanes pharmacokinetics and toxicity, as well as suggestions for personalized medicine's future path[9].

M.K. DeGorter et al. studied the drug-drug transporters are all now generally recognized as key factors of drug absorption, excretion, and, in so many circumstances, drug entrance into target organs. There was also a better understanding of how changes in drug transporter function, whether caused by genetic polymorphisms, drug-drug interactions, or environmental variables like dietary components, can lead to unanticipated toxicity. These impacts are due in large part to the interaction of several uptake and efflux transporters having overlapping functional capacities, which can result in significant intra - individual variability in drug disposal in vivo. We evaluate transporters from the solute carrier and ATP-binding cassette super families that are important in drug therapy and explain how greater understanding their expression, function, but also genetic variation will lead to better drug design and tissue targeting strategies, and also a reduction in the risk of drug-drug interactions and adverse drug reactions[10].

3. DISCUSSION

Oral chemotherapy's effectiveness is dependent on its ability to overcome various bioavailability obstacles at the absorption site, in the liver, and in the target structures. P-gp acts as a primary xenobiotic entry barricade. While P-gp is not the primary driver of oral obtainability, it is perhaps the most important determinant for some medicines. In theory, oral administration of an efficient reversal agent may block intestinal P-gp, resulting in enhanced oral bioavailability of a co-administered pharmaceutical. The physician will have to balance the total risk of side effects against potential benefits, the availability of alternative therapy, and the price. Clinicians will also have to make a judgment based on risk assessments obtained from big, population-based research in the actual world. However, during that time, this information is unavailable.

4. CONCLUSION

For more than 50 years, conventional anticancer medicines have been utilized to treat a variety of malignancies. The unexpected inter individual heterogeneity in effectiveness and toxicity associated with the use of these medicines is a significant restriction. The etiology and severity of the illness being treated, the possibility of unexpected medication interactions, and impairment of hepatic and renal function, or both, are all potential explanations of such heterogeneity in therapeutic effects. Despite the potential relevance of these clinical factors in predicting medication effects, it is well acknowledged that genetic variations in metabolism and excretion into faces and urine can have an even larger impact on effectiveness and toxin levels. The impact of each polymorphism is difficult to establish because the same medication could be used as a substrate for a variety of proteins and carriers. The consequences of many polymorphisms may be more clinically significant, but they are harder to measure methodologically. Clinical validation might potentially be aided by incorporating pharmacogenomics into phase II clinical trial design.

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