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Review Article

Advances in pharmacogenomic studies of docetaxel-a review

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Abstract: Docetaxel is currently utilized in the treatment of breast cancer, non-small cell lung cancer, prostate, and a variety of other cancers. However, there exists a significant difference in individual drug sensitivity and toxicity. In this paper, we review the genetic variation of drug metabolism related genes, correlations between the genetic polymorphisms of CYP450, ABC, SLCO1B3, and GSTs, as well as the clinical efficacy and adverse drug reactions of docetaxel, in order to provide a theoretical basis for an individualized approach to medical management.

Keywords: Docetaxel, gene polymorphism, CYP450, ABC, SLCO1B3, GSTs, individualized treatment

Introduction

Docetaxel, the generic of Taxotere, has been approved by the FDA since 1996 for the treatment of various cancers, such as breast cancer, non-small cell lung cancer, and hormone-dependent metastatic prostate cancer [1]. Its mechanism of action involves inhibition of tubulin depolymerization and hence cellular karyokinesis; arrested cells eventually undergo apoptosis [2].

Unfortunately, the high risk of adverse reactions to taxane therapy remains the main limitation in its application and typically necessitates a reduction in dosage or a change in treatment regimen altogether. Toxicity of paclitaxel, which possesses a mechanism of action similar to docetaxel, differs obviously among patients and remains a clinically relevant problem with great implications on their quality of life. Significant variability in paclitaxel clearance may contribute to the unpredictability of clinical outcomes. The appropriate initial dosage is determined by body surface area (BSA), and individual therapeutic, toxic, and side effects of this single drug administered as first-line treatment vary greatly. The metabolism of paclitaxel is non-linear; the bioavailable drug dose remains disproportionate with the drug concentration as time passes. These factors contribute to bone marrow suppression and neurotoxicity seen with paclitaxel use [3]. Toxicity can result in dose delay, dose reduction or even early cessation of treatment.

Unpredictable, interindividual variation in drug efficacy is a major challenge in docetaxel therapy as well. Renal and hepatic impairment, severity of disease, drug interactions and variability in disease pathogenesis are all responsible for the variation. Despite the potential effects of these variables on the determination of efficacy and toxicity of docetaxel, it is recognized that a single nucleotide polymorphism (SNP) similar to those controlling the genetics of drug metabolizing enzymes and transporters is an important contributing factor to medication tolerance and efficacy [4]. The genotyping of SNPs can be utilized to judge the efficacy of drugs on patients and select the most appropriate chemotherapeutic agent [5]. Pharmacogenomics focuses on the genetic characteristics of individual differences in drug adsorption, transfer, metabolism, and clearance, as well as on the different responses of patients to drugs due to genetic mutation. Importantly, pharmacogenomic data may be further used to guide

clinical management of patients in a more individualized manner [6].

Influence of CYP450 genetic polymorphism on docetaxel response

Metabolism of docetaxel is mainly influenced by the cytochrome P450 enzyme (CYP450). CYP450 is a group of isoenzymes coded by a structurally and functionally related supergene family, mainly located in the microsomes of hepatic cells. A specific enzyme responsible for drug oxidation and reduction, CYP450 not only inactivates docetaxel, but also catalyzes the drug into active metabolites. More than 90% of drug metabolism depends on hepatic microsomal cytochrome P450 enzymes. The group contains 58 genes and 29 pseudogenes, and belongs to 42 isoenzyme families in 17 gene families, among which enzymes from 3 gene families (CYP1, CYP2 and CYP3) are involved in biotransformation of the drug. A variety of factors, mostly genetic, lead to interindividual P450 gene variants, resulting in differences in P450 enzyme activity and eventually producing obvious differences in metabolism.

CYP1 and docetaxel

The CYP1 family includes CYP1A1, CYP1A2 and CYP1B1. CYP1B1 can only be detected in cancerous tissues and includes 3 genotypes [7]: CYP1B1-4326C>G SNP, increasing catalysis activity of CYP1B1; CYP1B1-142C>G SNP, increasing CYP1B1 expression; and CYP1B1-4390A>G SNP, increasing CYP1B1 degradation and decreasing protein expression. [please explain the meaning of this paragraph].

Greater numbers of researchers believe that CYP1B1 is related to the chemosensitivity of docetaxel. Pastina et al. [8] found that when docetaxel was used to treat emasculate prostate cancer, the efficacy of patients homozygous to CYP1B1-4326C>G was low, with short progression-free survival (PFS) and overall survival (OS). Rizzo et al. reported that [9] when paclitaxel was used to treat breast cancer, the probability of anaphylactic reaction occurrence in patients with the CYP1B1-4326C>G (CYP-1B1*3) allele was relatively low. Vasile et al. [10] found that when docetaxel was used to treat patients with advanced non-small cell lung cancer as a single drug therapy, CYP1B1-4326C>G SNPs were related with PFS and OS (how were they related?). We believe [who believes? needs a reference if not you] that the genetic locus could be utilized in predictive indexing for observing the efficacy of docetaxel on non-small cell lung cancer.

CYP2 and docetaxel

CYP2 is recognized as the largest of the cytochrome P450 isoenzyme families, including subfamilies such as CYP2A, CYP2B, CYP2C, and CYP2D. Dai et al. found that the genetic variants of CYP2C8 were CYP2C8*2 and CYP2C8*3. Compared with wild type CYP2C8*1, CYP2C8*2 decreased the clearance rate of paclitaxel, while the metabolic activity of CYP2C8*3 was only 15% of the wild type. Later experiments also revealed the metabolic activity of paclitaxel to be decreased under two gene variants (which variants?) [11, 12]. However, SNPs of CYP2C8 have not been found in the Asian population to date. Bergmann et al. [12] reported that clearance rates of docetaxel in patients with ovarian cancer carrying CYP2C8*3 were significantly lower than in wild type patients ($P<0.05$). Toshitaka [13] studied female patients with reproductive system tumors who were treated with docetaxel, finding that only CYP39A1 was related with a decrease in neutrophils [neutrophils are granulocytes. neutropenia can be Grade 4. What is the meaning here?], and that adverse reactions more easily occurred in patients with A/A and A/T type.

CYP3 and docetaxel

CYP3A subfamilies are composed of CYP3A4, CYP3A5, CYP3A7 and CYP3A43. In Han Chinese, there are 14 folds of difference among individuals with an active CYP3A enzyme [14]. Paclitaxel is mainly catalyzed by CYP3A4/5, and via hydroxylation, it is excreted with bile [11]. Differences in CYP3A/5 genotypes can therefore influence the metabolism of paclitaxel. CYP3A4 is the main CYP protein expressed in the adult liver. It has been reported that CYP3A4*1B mutation leads to decreased enzyme activity of CYP3A4, with occurrence frequencies in Caucasian, African and Asian being 9%, 53% and 0%, respectively. From a total of 39 SNPs, CYP3A4*4, *5, *6, *18 and *19 have been confirmed in Chinese. However, it is reported that their polymorphisms have no significant influence on CYP3A4 activity. The

possible reason for this is that in the investigated population, the frequency of this allele is very low, and the change of function is also small [15]. Recently, it has been proposed that the mechanism of CYP3A4 species and individual differences in drug metabolism might be closely related with the pregnane X receptor (PXR), and that the drug (paclitaxel or docetaxel?) regulates the expression of CYP3A4 via PXR [15, 16].

CYP3A5 is mainly expressed in extrahepatic tissues such as the intestinal wall, kidney, pancreas, prostate, and lung. CYP3A5 expression is not controlled by the nuclear receptor PXR/SXR, with SNP being the main regulatory variable of CYP3A5 expression. The correlation of polymorphisms between CYP3A4 and CYP3A5 is also very important (why?). Linkage disequilibrium, haplotype analysis and functional analysis of transcription factors remain to be studied in detail.

Influence of ABC protein gene polymorphism on docetaxel response

Drug membrane transport proteins are very important in the metabolic processes of taxoids. ATP-binding cassette (ABC) proteins (ABCB1, also named MDR1, and ABCC2, also named MRP2) [17] are a group of taxoid transporters. P-glycoprotein (P-gp) is coded for by multidrug resistant gene ABCB1. It is also a membrane protein, belonging to the ATP binding family, which is mainly expressed in hepatic, intestinal, bile duct, and tumor tissues, as well as endothelial cells of the blood brain barrier [18]. The main physiological function of ABC transporters is to protect normal cells and tissues from environmental toxins; in turn, this also affects the pharmacodynamic properties of anticancer drugs in the human body. Genetic mutations may affect the rate of drug elimination via bile and likely lead to the widespread presence of such transporters in tissues. Mutations of ABC proteins lead to multidrug resistance by decreasing effective intracellular concentrations of drugs.

ABCB1 and docetaxel

The ABCB1 gene is expressed mainly in the intestines, liver, kidney and vascular endothelial cells, and participates in a variety of secretion, absorption, distribution and excretion functions. It has been reported that there are at least 50 SNPs and 3 insertion/deletion polymorphisms in the ABCB1 gene [11]. The gene polymorphisms of C1236T, G2677T/A C3435T in exons 12, 21 and 26 are closely related with the function and expression of P-gp [19]. Different SNPs can significantly influence the efficacy and occurrence of adverse reactions to paclitaxel [10, 20]. Vaclavikova et al. [21] found that the expression level of the ABCB1 gene in 79.5% of carcinomatous tissues was down-regulated, and related with polymorphic mutation of C3435T and C1236T; that is, the ABCB1 SNP could change the function of P-gp by influencing its expression. The presence of the ABCB1 C3435T mutant allele significantly correlated with a great decrease in neutrophils (P=0.03) [22]. Of Asian patients with nasopharyngeal carcinoma treated with paclitaxel, those with ABCB1 2677 GT and ABCB1 2677 TA genotypes had significantly lower hemoglobin levels compared to those of ABCB1 2677 GG and ABCB1 2677 TT genotypes [23]. Lal et al. [24] found that compared with CT-GT-CT and TT-TT-TT mutants, CC-GG-CC wild type patients with C1236T, G2677T/A, and C3435T genotypes exhibited a significantly increased clearance rate of paclitaxel in vivo, with the plasma peak drug concentration significantly decreased. Fransson's group reported that SNPs had a small influence on the plasma concentration of paclitaxel [25]. However, even a slight change of transfer or metabolism would also affect the concentration of the main metabolic products of paclitaxel. Effects of the ABCB1 gene on toxicity is of greater importance than the pharmacokinetics of the drug themselves. In a study exploring the relationship between gene polymorphisms and clearance rates of paclitaxel in Caucasian female patients with ovarian cancer [26], it was found that clearance had no significant correlation with ABCB1 C1236T or its variants. Evidence suggests that the ABCB1 gene polymorphism is important in docetaxel metabolism and function, but whether the polymorphism can be utilized as a predictive index remains to be determined.

ABCB2 and docetaxel

The ABCC2 gene is expressed in capillary bile duct film, cerebrovascular endothelial cell membranes, small intestinal mucosa and placental trophoblast tissue. Expression of the

ABCC2 gene plays a very important role in a [remitting multidrug hold]? to anti-cancer drugs. In the context of extremely low oral bioavailability and little variation of exposure levels between patients, experiments utilizing Mrp2 -/- mice revealed ABCC2 to exhibit a great influence on the pharmacokinetics of docetaxel. The bioavailability of administering docetaxel orally to wild-type mice was increased by 10%, yet that of Cyp3a/Mdr1a/b/Mrp2 mice was increased by 73% [27]. The Biobank Project in Japan found that Grade 3 or 4 leukopenia/neutropenia caused by docetaxel therapy might be related with the ABCC2 polymorphism (C28-548T, A68231G, C101620771G, C1016352-09T) [28]. Randomized trials in patients with ovarian cancer in Scotland revealed that the ABCC2 G1249A polymorphism replaced valine with isoleucine. Muscle and joint pain were found to correlate obviously with polymorphisms (ABCC2 T3563A) [29]. The study, however, did not investigate elimination processes of paclitaxel. Area Under the Curve (AUC) evaluation revealed bioavailability of Abcc2-/- mice to be increased 1.3 times, bioavailability of Abcb1a/1b-/- mice also increased 1.3 times, and bioavailability of Abcb1a/1b-/- and Abcc2-/- mice, which lack these two kinds of transporters, increased 1.7 times. These findings illustrate that the transport effect of ABCC2 and ABCB1 genes on paclitaxel was both independent and mutual [29]. More experimental data is required for ABCC2 to be considered as a marker reflective of pharmacokinetic changes and a side effect profile of paclitaxel.

Influence of SLCO1B3 gene polymorphism on response to docetaxel

The solute vector superfamily is mainly responsible for the uptake and transfer of drugs, and organic anion transporting polypeptides (OATPs) coding transport proteins composes one of the most common drug transporter families [30]. In the six big families included in OATPs, OATP1B3 has been demonstrated to transfer docetaxel. OATP1B3 is termed OAPT-8, or liver specific organic anion transporter (LST-2), and is located in hepatocyte membranes, responsible for transporting internal and external material of the sanguis into hepatocytes for regulation of metabolism. In the SLCO1B3 polymorphic genes related with OATP1B3 transport activity, 334T>G and 699G>A possess significant linkage disequilibrium, and greatly influence the transport activity of OATP1B3 [31].

In 92 blood samples from patients of different races with cancer, Choi et al. [31] found that race specificity of SLCO1B3 was strong, and that mutation frequencies in Caucasians and Chinese were 71%~90%, while that of Blacks was 41%. Furthermore, the polymorphism of SLCO1B3 was significantly correlated with drug efficiency. deGraan et al. [32] reported that after using docetaxel in 141 Caucasian patients with tumors, it was found that patients with defective OATP1B1 and OATP1B3 genes exhibited a significantly decreased rate of clearance. In terms of adverse drug reactions, Kiyotani et al. [28] reported that in the Japanese population, severe granulocytopenia caused by application of docetaxel was related to SLCO1B3 polymorphism. Yamada et al. [33] demonstrated that the in vivo absorption of docetaxel was mainly related to OATP1B3. However, Lewis et al. [34] reported no obvious correlation between treatment-related granulocytopenia and SLCO1B gene polymorphisms in Japanese people, as found in studies. Perhaps such findings are due to inherent errors in experimental design and small sample size utilized. Baker [35, 36] also indicated that, in Spanish cancer patients, neurotoxicity induced by paclitaxel had no important correlation with SLCO1B3 genotype.

Influence of GST gene polymorphism on docetaxel response

Glutathione S-transferases (GSTs) belong to the multi-functional poly-2 protein family, which is the most important phase II metabolic enzyme family in the human body. This dimeric protein has a variety of physiological functions, catalyzing electrophilic material and combining substrates with glutathione. It also can combine and lipotropy cytotoxic agents to enhance their solubility, promoting drug excretion and reducing their effects in the body. However, tumor cells can express GSTs to protect themselves from the damage of chemotherapy drugs, leading to tumor resistance of drugs. Of the GST encoding genes, GSTM1, GSTT1, GSTP1 and GSTA1 exhibit a polymorphic distribution in the general population to such an extent that polymorphic mutation changes how

corresponding enzymes detoxify heterogeneous substrates. Because of high deletion rates of GSTM1 and GSTT1 in various racial populations, the enzyme function is invariably lost. Furthermore, the deactivation capacity of the enzyme on the drug and intermediate metabolites is decreased. In our clinical study on patients with breast cancer receiving paclitaxel chemotherapy, it was demonstrated that the chemotherapeutic efficacy was better in patients with GSTM1 deletion types and/or those carrying a GSTP1 (I105V) mutation [37]. GSTP1 A313G (I105V) is another gene polymorphism variation with a high incidence in GSTs. Further study of GSTs and taxane drug resistance is required for further mechanistic elucidation.

Discussion

Because of the genetic polymorphisms of metabolic enzymes and associated transport proteins, the pharmacokinetics and pharmacodynamics of docetaxel are very unstable. Studies on the pharmacogenomics of docetaxel explain the molecular mechanisms of individual differences in drug efficacy. Most of the aforementioned studies focused on therapeutic effects and less on safety. Currently, although experiments have demonstrated that relevant genetic polymorphisms during drug metabolism and transport will lead to changes in efficacy, a long way remains to guiding clinical therapy. The main reasons are as follows: 1. Due to polymorphisms, the effects of drugs on different races, individuals or tumors due to polymorphism are different or even opposite. Therefore, analyses with large sample sizes are necessary. 2. Testing methodology, as well as data and standardization of analytical information guarantees accuracy, compatibility and reliability of data intended for clinical use. 3. Because most of the aforementioned studies focused on the single phase SNP of a specific gene, genetic mutation in all metabolic or pharmacologic pathways require further study; predictive accuracy rates would increase in concert with the detection index. 4. The relationship between genotype and phenotype is relatively complicated. 5. There are interactions among chemotherapeutic agents targeting breast cancer, and differences in tolerance exist among individuals. The application of non-linear pharmacodynamic characteristics by paclitaxel combined with other drugs possesses sequential dependency and pharmacological effects.

In addition, it is also worth noting that combining enzyme probe and therapeutic drug monitoring (TDM) to guide the individualized medication (may do what?). Utilizing enzyme probe detection of metabolic enzyme activity directly and determining an appropriate initial drug dosage may determine how to achieve desired drug concentrations. Testing the concentration of the drug and its metabolites in the blood by TDM, constructing the most appropriate dosage regimen, and adjusting the level of drug concentration in the body in a target area are all worthwhile objectives of TDM. Docetaxel individualized regimens will be realized by combining the three kinds of technology, so as to reduce as much as possible the occurrence rate of ineffective treatments or adverse reactions.

It is believed that with a deeper exploration and solution of these problems, that studies concerning pharmacogenomics will be successfully applied to guide clinical, individual anti-tumor therapy. Future studies should consider researching combinations of multi-genes, and utilize data from a large, multi-center and multiracial clinical sample size. Individualized treatment regimens utilizing docetaxel will eventually be commonplace.

Future perspective

Pharmacogenomic studies of docetaxel can help elucidate the molecular mechanism responsible for individual differences in efficacy and toxicity. Judging the risk-benefit ratio of docetaxel by detecting SNP genotypes of different patients, it may become possible to guide clinical management. As the field of personalized genetics matures, application of pharmacogenomics will eventually become commonplace and will be used to guide clinical individualized anti-cancer treatment.

Disclosure of conflict of interest

None.

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