

Pharmacogenetics in breast cancer: steps toward personalized medicine in breast cancer management

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Abstract: There is wide individual variability in the pharmacokinetics, pharmacodynamics, and tolerance to anticancer drugs within the same ethnic group and even greater variability among different ethnicities. Pharmacogenomics (PG) has the potential to provide personalized therapy based on individual genetic variability in an effort to maximize efficacy and reduce adverse effects. The benefits of PG include improved therapeutic index, improved dose regimen, and selection of optimal types of drug for an individual or set of individuals. Advanced or metastatic breast cancer is typically treated with single or multiple combinations of chemotherapy regimens including anthracyclines, taxanes, antimetabolites, alkylating agents, platinum drugs, vinca alkaloids, and others. In this review, the PG of breast cancer therapeutics, including tamoxifen, which is the most widely used therapeutic for the treatment of hormone-dependent breast cancer, is reviewed. The pharmacological activity of tamoxifen depends on its conversion by cytochrome P450 2D6 (CYP2D6) to its abundant active metabolite, endoxifen. Patients with reduced CYP2D6 activity, as a result of either their genotype or induction by the coadministration of other drugs that inhibit CYP2D6 function, produce little endoxifen and hence derive limited therapeutic benefit from tamoxifen; the same can be said about the different classes of therapeutics in breast cancer. PG studies of breast cancer therapeutics should provide patients with breast cancer with optimal and personalized therapy.

Keywords: pharmacogenomics, genetic, pharmacokinetic, pharmacodynamic, personalized medicine, pharmacotherapy, anticancer drugs, efficacy, safety

Introduction

Breast cancer is the most common form of cancer and the second-leading cause of cancer-related death in women.¹⁻³ It is estimated that there will be 192,370 new cases of breast cancer diagnosed in 2009, accounting for 27% of all new cancer diagnoses.³ Certain heritable genetic factors may increase breast cancer risk, with susceptibility loci including high-penetrance genes that are rare (eg, BRCA1/2), as well as moderate-penetrance and low-penetrance genes and loci. Studies of these susceptibility loci have been critical to our understanding of the biological mechanisms of breast cancer. These studies have also been instrumental in shifting the focus in breast cancer research toward genetic and pharmacogenomic (PG) studies, in the hope that determination of individual genetic profiles in relation to these genes and loci will allow for targeted therapies to maximize therapeutic benefit.

Breast cancer is a heterogeneous disease, manifesting as different molecular subtypes, each of which responds to chemotherapeutic agents and radiation differently.² Some of the currently available chemotherapy drugs for breast cancer management

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include tamoxifen, aromatase inhibitors, fulvestrant, anthracyclines, taxanes, cyclophosphamide, vinorelbine, platinum, trastuzumab, lapatinib, bevacizumab, and others. Until very recently, the selection of treatment was almost exclusively based on the characteristics of the tumor, such as the presence of estrogen receptor (ER) or HER-2 receptor expression, with minimal emphasis on the patient's genetic make-up.⁴ The use of genomic profiles to assess the risk of tumor recurrence, drug resistance, and drug toxicity could be tremendously useful in breast cancer management. For instance, several studies have shown that patients with the cytochrome P450 enzyme 2D6 (CYP2D6)*4 allele, which causes a decrease in the enzymatic activity of CYP2D6, benefit less from tamoxifen therapy. Studies of aromatase inhibitors have shown that patients carrying a certain polymorphism in the aromatase gene may be at increased risk of osteoporosis. PG studies of breast cancer therapeutics can guide health care providers toward personalized medicine, providing patients with breast cancer with optimal individualized therapy.¹⁻⁷

PG and personalized medicine

PG is the study of how genetic inheritance influences a person's response to drugs.⁵ Clinical observations of inherited differences in drug effects were first documented in the 1950s, giving rise to the field of pharmacogenetics and subsequently PG.⁶ PG uses genome-wide approaches to investigate the inherited basis of differences in drug responses in the interest of developing novel drugs and therapies.⁷ An understanding of the influence of genetics on efficacy or toxicity of a drug could potentially lead to the development of a personalized drug treatment algorithm based on an individual's genetic make-up.^{5,8,9} PG studies involve the application of molecular biology, high-throughput biotechnology, and bioinformatics in order to create customized drug treatments for a particular individual or patient population.¹⁰ The ultimate goal of PG is to customize drugs for a defined patient population so that the right drug is given at the right dose to the right person. In the future, the "one-drug-fits-all" approach to treating a particular disease and the "trial-and-error" approach to prescribing medications will be replaced by highly specific, "tailor-made" prescriptions based on the genetic makeup of an individual.⁵

Single nucleotide polymorphisms

The most common type of DNA variation in the human genome is the single nucleotide polymorphism (SNP).⁶ SNPs represent natural genetic variability in the human genome

and are considered the major genetic source of phenotypic variability that differentiates individuals within a given species. They can occur in noncoding regions and in coding regions. The latter often generate polymorphic variation in expressed proteins, affecting their functional properties. If the SNP occurs in the promoter region of a gene, it may change the binding site for transcription factors and thus alter the regulation of expression.¹¹ The allelic frequencies of a given SNP may be different in different populations. Because an SNP is present every 300–1,000 bases in man, there are several million possible nucleotide positions in the human genome at which there could be degrees of natural variation.¹² It is believed that SNPs could be used to identify genes that contribute to population-wide, polygenic diseases. At present, information leading to a better understanding of genetic variability is an intense area of focus. The goal is to identify genes that contribute to disease, may be targets for new therapies, and may predict the outcome and side effects of a given therapy (Table 1). High-throughput technologies such as DNA microarrays are anticipated to serve as comprehensive tools for the development of accurate predictive genetic markers of treatment outcomes for many disease states.¹³ Health care providers should be prepared for a future in which these technologies will be used on a routine basis to optimize clinical outcomes.

Genetic polymorphisms that influence the pharmacokinetics and pharmacodynamics of breast cancer therapeutics

The field of pharmacogenetics initially focused only on drug metabolism, but now encompasses the spectrum of the drug delivery process, including transporters that influence drug absorption, distribution, and excretion.¹⁴ There are more than 30 families of drug-metabolizing enzymes in humans, all of which have genetic variants that may result in functional changes in the protein encoded. The study of polymorphisms in genes that encode drug-metabolizing enzymes, transporters, or targets can be used to predict the toxicity and response to pharmacologic agents that are used in breast cancer treatment.¹⁵ Transporter proteins have a significant role in regulating the absorption, distribution, and excretion of many of these pharmacologic agents.¹⁴ Members of the adenosine triphosphate (ATP)-binding cassette family of membrane transporters, for example, are among the most extensively studied transporters involved in drug transportation and

Table 1 SNPs for key therapeutic classes in breast cancer

Therapeutic class	Gene/polymorphism	PK application	Clinical outcomes	References
Endocrine				
Tamoxifen	CYP3A4*1B	Increased CYP3A4 expression		22
	CYP3A5*3C		Possible association with improved RFS	28
	SULT1A1*2	Decreased enzyme activity	Possible association with increased ROD	32
	SULT1A1*1		Possible association with decreased ROR	33
	UGT2B15*2		Possible association with decreased 5-year survival rates	28
	CYP2D6*3/*4/*5/*6	Poor Metabolizers	CYP2D6*4 possible association with worse RFT, RFS, and BCR	5, 36
	CYP2D6*10/*17/*41	Intermediate metabolizers	CYP2D6*10/*41 possible association with worse RFT, ROR, and BCR	26
	ER d5	Loss of exon 5	Possible association with tamoxifen therapy failure	40
CCND1/PAK1	Over-expression	Possible association with shorter RFS; PAK1 also may reduce benefit of tamoxifen	41, 42	
Aromatase inhibitors				
	CYP19A1 polymorphisms Cys264, Thr364, *Arg39Cys264 rs4646	Decreased enzyme activity	Possible association with letrozole resistance	50–54
			Possible association with increased TTP and letrozole response	45
	CYP19A1 (1531C>T)		Possible association to osteoporosis	50
Chemotherapy agents				
Taxanes	CYP1B1*3		Possible association with better PFS and better complete response	52, 53
Vinorelbine	ABCB1 3435C>T, CYP2D6*4, CYP3A*3, CYP3A5*3		Possible association with vinorelbine response	64, 66
Cyclophosphamide	CYP3A4*1B, *CYP3A5*1		Possible association with survival and ovarian failure	70, 71
	CYP2B6*6	Higher clearance and shorter half-life of cyclophosphamide		77, 78
	CYP2B6 (–2320C>T, –705T>C, 18492C>T)		Possible association with leukopenia	81
Antimetabolites				
	MTHFR 1298 MTHFR C677T TYMS TSER	Decreased enzyme activity Decreased enzyme activity	Possible association with poorer survival rate Possible association with better survival time Association with survival	80
				90
				90, 91
				93
Gemcitabine				
	CDA A70T	Decreased gemcitabine clearance	Possible association with neutropenia	84, 85
	RRM1 (–37C, –524T)		Possible association with better tumor response, PFS, and OS	86, 87
Anthracyclines				
Doxorubicin	CBR3 11G>A		Possible association with increased tumor reduction and hematologic toxicity	98
	ABCB1 3435T		Possible association with better clinical response	100, 101
	SLC22A16 146A>G	Increased exposure to doxorubicin		99
Epirubicin	NQO1 556C>2, NQO1*2		Possible association with drug response and survival outcomes	105

(Continued)

Table 1 (Continued)

Therapeutic class	Gene/polymorphism	PK application	Clinical outcomes	References
Platinums				
	GSTM1 deletion		Possible association with increased median survival time	5, 6, 95
	MET1F G-7T	Lower platinum concentration	Possible association with shorter survival	95
	ERCC1 N118N		Possible association with median survival time and TTP	5, 6, 95
Targeted therapy				
Trastuzumab	Fc- γ RIIIA-158 V/V, Fc- γ RIIa-131 H/H		Possible association with objective response rate and PFS	107

Note: *indicates CYP allele.

Abbreviations: PK, pharmacokinetic; MTHFR, methylenetetrahydrofolate reductase; RFS, recurrence free survival; ROD, rise of death; ROR, risk of relapse; RFT, relapse free time; BCR, breast cancer relapse; TTP, time to progression; PFS, progression free survival; OS, overall survival.

distribution. P-glycoprotein, a specific member of the ATP-binding cassette family, is encoded by *ABCB1*, also known as *MDR1*.¹⁶ The function of P-glycoprotein is the energy-dependent cellular efflux of substrates. Bilirubin, anticancer agents, cardiac glycosides, immunosuppressive agents, glucocorticoids, human immunodeficiency virus (HIV) type 1 protease inhibitors, and many other medications have been shown to be targets of P-glycoprotein. The expression of P-glycoprotein in many normal tissues suggests that it has a physiological role in the excretion of xenobiotics and metabolites into urine, bile, and the intestinal lumen. Of course, transportation is only one part of the full spectrum of drug delivery, albeit a crucial one. A better understanding of how polymorphisms in genes encoding transporters, metabolizing enzymes, and receptors affect drug efficacy and toxicity is an important step toward making the clinical practice of pharmacogenetics a reality.

Cancer therapeutics

This section will discuss the classes of drugs currently used in the treatment of breast cancer, including their pharmacokinetic (PK) and pharmacodynamic (PD) properties, and SNPs that influence the uptake and metabolism of the drugs, as well as drug response and clinical outcomes associated with specific SNPs.

Hormonal/endocrine therapies

Tamoxifen

Tamoxifen binds selectively to estrogen receptors (ERs) and is, therefore, indicated for patients who express ER and whose tumors are endocrine-sensitive. It has been extensively used in patients with breast cancer for the last 30 years.⁹

Tamoxifen is a prodrug that is metabolized by members of the cytochrome (CYP) P450 family into 2 active metabolites:

4-hydroxy tamoxifen (4OH-TAM) and 4-hydroxyl-N-desmethyl-tamoxifen (endoxifen). CYP3A4/5 is responsible for the conversion of tamoxifen into N-desmethyl-tamoxifen, which is then converted into its active metabolite, endoxifen, by CYP2D6. CYP2D6 is also responsible for the conversion of tamoxifen into 4OH-TAM. The active metabolites of tamoxifen then undergo sulfation via sulfotransferase (SULT1A1) and glucuronidation via uridine diphosphate (UDP)-glucuronosyltransferase (UGT2B15) leading to excretion.^{17,18}

The accepted dose of tamoxifen is 20 mg/d. However, in a recent study of steady-state levels of tamoxifen and active tamoxifen metabolites, there was interpatient variability for all 3 metabolites.⁹ These results suggest that the general recommended dose of tamoxifen may not be optimal for all patients and hence PK monitoring might be of great value.

An additional consideration for tamoxifen treatment is that hot flashes, a common side effect of tamoxifen therapy, occur in 50%–70% of patients treated with tamoxifen. It is not possible to simply treat these hot flashes with exogenous estrogen. However, it has been found that some patients respond to selective serotonin reuptake inhibitors (SSRIs), which inhibit CYP2D6.^{19,20} Thus, concomitant administration of CYP2D6 inhibitors, like the aforementioned SSRIs, may affect breast cancer outcomes with tamoxifen therapy through conversion of a potent metabolizer to a phenotypically poor metabolizer (PM). Examples of potent CYP2D6 inhibitors include the antidepressants fluoxetine, paroxetine, and venlafaxine; moderate or weak inhibitors include cimetidine, amiodarone, ticlopidine, and haloperidol.¹⁹ There is also the possibility that other CYP isoforms such as CYP2C19 might potentially catalyze the formation of tamoxifen metabolites beyond those generated by CYP2D6.²¹

Related SNPs

CYP3A4

CYP3A4 is involved in the metabolism of over 60% of currently used chemotherapy drugs. Therefore, it plays a significant role in clinical settings. A common SNP of CYP3A4 is CYP3A4*1B (−392A>G), which is associated with increased CYP3A4 expression. However, to date, the clinical significance of CYP3A4 polymorphisms is unknown.²²

CYP3A5

The most common variant of CYP3A5 is CYP3A5*3C (IVS3-327A>G, 6986A>G). This polymorphism results in a splicing defect and an absence of CYP3A5 protein.^{23,24} Three separate studies have failed to show any association between CYP3A5*3C and tamoxifen metabolism or clinical outcomes.^{25–27} However, in a study involving 677 patients with postmenopausal breast cancer randomized to either 2 or 5 years of tamoxifen, it was found that patients in the 5-year treatment group who were homozygous for CYP3A5*3 had significantly improved recurrence-free survival ($P = 0.002$). CYP3A5*3 homozygous patients in the 2-year treatment group showed an increased risk of recurrence, but this was not statistically significant ($P = 0.15$).²⁸ These results justify progression to large population studies of relevant clinical outcomes associated with this SNP.

SULT1A1

Three polymorphisms in SULT1A1 have been identified: SULT1A1*1, SULT1A1*2, and SULT1A1*3. The most common polymorphism, SULT1A1*2, results in decreased enzymatic activity of SULT1A1 due to a shorter protein half-life. The effect is decreased sulfation of 4OH-TAM.^{29–31} The clinical relevance of SULT1A1*2 was investigated in a study including 337 patients with breast cancer receiving tamoxifen therapy. Patients who were homozygous for SULT1A1*2 had an almost a 3-fold increase in risk of death as compared to patients who had a common allele or who were heterozygous (SULT1A1*1/SULT1A1*2).³² A separate study involving 226 patients with breast cancer found that individuals who were homozygous for SULT1A1*1 had a decreased risk of recurrence.³³ A subsequent study, however, found no association between SULT1A1 polymorphisms and tamoxifen or its metabolites.²⁶ Copy number variation might be more important for functional variations in SULT1A1 activity than nonsynonymous SNPs.³⁴

UGT2B15

UGT2B15*2(253G>T; D85Y) is a nonsynonymous polymorphism of UGT2B15. A 2005 retrospective study involving 165 patients analyzed SULT1A1, UGT2B15, and CYP2D6 polymorphisms. The study found that patients carrying the SULT1A1*2 variant and at least one UGT2B15 allele had significantly reduced 5-year survival rates.³⁵ However, another study looking at the association of UGT2B15*2 with tamoxifen and clinical outcomes found no association.²⁸

CYP2D6

More than 80 allelic variants of *CYP2D6* have been identified and grouped into 4 categories: poor, intermediate, extensive, and ultra-rapid metabolizers.⁵ Poor metabolizers (PMs) are subjects who have inactive enzyme, deletion of the *CYP2D6* gene, or loss of functional alleles of CYP2D6. The nonfunctional variants of CYP2D6 are CYP2D6*3, CYP2D6*4, and CYP2D6*6; enzyme is absent in carriers of the CYP2D6*5 variant.

CYP2D6 SNPs represent a good example of population-based variations in SNP frequency. Five to 10% of Caucasians are PMs, with the CYP2D6*4 allele present in 70%–90% of the population, while this allele is rare in Asians and black Africans.⁵ In Asians, the CYP2D6*10 allele is a major polymorphism, resulting in an intermediate metabolizer (IM) phenotype. This phenotype is present in 38%–70% of Asians and 20%–34% of Africans, but is rare in Caucasians. Individuals with an IM phenotype have somewhat reduced *in vitro* activity of CYP2D6 enzymes.⁵

In contrast to PMs and IMs, ultra-rapid metabolizers carry gene duplications or multiduplications that result in increased enzymatic activity. Variant alleles in this category include CYP2D6*2XN, CYP3A4*1B, and CYP3A5*3. These variants are rare in Caucasians and Asians, but common in Ethiopians and Saudi Arabians. The identification of ultra-rapid metabolizers may help in the selection of patients who will benefit from a longer period of tamoxifen use (up to 4–5 years) before switching to aromatase inhibitors.

The enzymes responsible for elimination and inactivation of tamoxifen and its metabolites through conjugation with either a sulfate or a glucuronide may also have important genetic variations. To date, however, studies have yielded conflicting data on the relationship between these variations and tamoxifen processing, highlighting the need for further studies.⁵

CYP2D6 SNPs have been well characterized. A recent study investigating the CYP2D6*4 allele, a PM that is

common in Caucasians, in patients being treated with tamoxifen found that individuals who were homozygous for CYP2D6*4 had significantly lower endoxifen levels than patients who had the wild-type gene; patients who were heterozygous for CYP2D6*3/*4/*5/*6 had intermediate levels of endoxifen.²⁶ Clinical outcomes in relation to CYP2D6*4 have also been investigated. An early study showed that patients with decreased levels of metabolism of tamoxifen had a significantly decreased time to recurrence ($P = 0.034$), worse relapse-free survival ($P = 0.017$), and a significantly higher risk of breast cancer relapse ($P = 0.007$) as compared with patients who had normal levels of metabolism.³⁶ The results of this study were confirmed in 2 subsequent studies of patients who were homozygous for CYP2D6*4. The first study included 190 patients with postmenopausal breast cancer treated with adjuvant tamoxifen. Women who were homozygous for CYP2D6*4 had significantly lower relapse-free and disease-free survival (DFS) and had a lower incidence of hot flashes as compared with women either with one or no CYP2D6*4 alleles.³⁷ The second study corroborated these results, demonstrating that homozygous patients receiving tamoxifen had a shorter relapse-free time and reduced DFS than patients with at least one wild-type CYP2D6 allele. However, no association with overall survival was found in this or a subsequent study of 162 patients with breast cancer.^{25,35} A related study of 226 patients with breast cancer demonstrated significantly improved survival in patients carrying CYP2D6*4 and SULT1A1*1 (wild-type) alleles.³³ Finally, a study involving 486 patients with breast cancer found that carriers of the CYP2D6 alleles *4, *5, *10, and *41 had a reduced relapse-free period ($P = 0.02$), poorer event-free survival ($P = 0.02$), and significantly increased recurrence.²¹ Overall, these results indicate that genotyping of patients with impaired CYP2D6 function may be beneficial in a clinical setting to determine which patients will derive the most benefit from adjuvant tamoxifen therapy.

ESR1/ESR2

ESR1/ESR2 encodes the target of tamoxifen, the ER. In a study of the occurrence and frequency of the exon 5 deletion variant (ER d5) of *ESR1/2*, the d5 variant was detected in both breast tumor tissue and normal tissue, indicating it is a naturally occurring polymorphism. Patients who relapsed within the first 15 months had increased levels of expression of d5 as compared with those who did not, indicating that increased ER d5 expression may result in relapse due to clonal expansion of tamoxifen-resistant tumor cells.³⁸

CCND1 and PAK1

Cyclin D1 (CCND1) and p21-activated kinase 1 (PAK1) have been implicated in the activation of ER expression. Jirstrom et al³⁹ found that over expression of CCND1 is associated with an increased risk of breast cancer recurrence and inversely linked to overall survival.³⁹ Another study investigating both CCND1 and PAK1 found an association between amplification of either one of these genes and shorter recurrence-free survival ($P = 0.025$). Reduced benefit from the drug was also demonstrated in patients with PAK1, but not CCND1 amplification.⁴⁰ Similarly, Lundgren et al⁴¹ demonstrated that amplification of CCND1 and PAK1 may be associated with tamoxifen response.

TP53

TP53 encodes p53, an important tumor suppressor that induces apoptosis. Wegman et al⁴² examined the P72 (215C>G) SNP of *TP53* and found that patients who had at least one TP53 codon 72 proline allele had a significantly better response to tamoxifen.⁴² Studies have also shown that the over expression of p53 is associated with poorer clinical outcomes and resistance to tamoxifen in premenopausal women with breast cancer.⁴³

Aromatase inhibitors

Aromatase inhibitors have proven efficacy in both advanced and early postmenopausal hormone receptor positive breast cancers. The predominant problem associated with aromatase inhibitors is musculoskeletal complaints reported by some users. This side effect can be debilitating and has led to discontinuation of aromatase inhibitor therapy in some cases. This difference in clinical response has prompted researchers to take a second look to see if there are pharmacogenetic differences among patients that might enable the identification of cases in which aromatase inhibitor therapy would be appropriate and safe.^{44,45}

Aromatase inhibitors inhibit the formation of estrogen in breast tissue and are used in advanced disease settings after 5 years of tamoxifen therapy.⁵ The target of aromatase inhibitors is the CYP enzyme aromatase, which is encoded by *CYP19A1*, also known as the aromatase gene. Aromatase inhibitors work by blocking the conversion of androstenedione and testosterone to estrone and estradiol in the periphery. As such, they are used in postmenopausal women since they will have no effect on the ovaries. Aromatase inhibitors can be classified into 2 groups: steroidal (exemestane) and nonsteroidal (letrozole and anastrozole), reducing cross-resistance between therapies and allowing prolonged use of

different inhibitors. The side effects of aromatase inhibitors are usually less severe and less frequent than tamoxifen.⁴⁶

Related SNPs

CYP19A1

More than 88 CYP19A polymorphisms have been identified, resulting in 44 haplotypes that vary widely among ethnic groups. A survey of 60 patients of Caucasian, African-American, Han Chinese American, and Mexican American ethnicity found that Cys264, Thr364, and double-variant Arg39Cys264 allozymes had significantly decreased activity as compared with the wild-type enzyme. The Arg39-Cys264 allozyme also exhibited a significantly increased inhibitor constant for letrozole. The frequencies of the Arg39 and Cys264 alleles varies among ethnic groups, with Cys264 occurring at a higher frequency in Han Chinese Americans (11.7%) and African-Americans (22.5%) as compared with Caucasian Americans (2.5%) and Mexican Americans (5%). The Arg39 variant was shown to be present at a frequency of 6.7% in Han Chinese Americans, but was rare in other ethnic groups. These results suggest that patients with decreased enzyme activity may not receive the full benefit of aromatase inhibitors.⁴⁷

Two separate Spanish studies examined the rs4646 polymorphism of CYP19A1. The first study including 67 patients with postmenopausal breast cancer receiving letrozole found that patients with the rs4646 polymorphism had an increased complete response rate and time to progression.⁴⁸ The second study including 94 patients also receiving letrozole therapy found that 8 polymorphisms, one of which included rs4646, could predict response to letrozole with 86% accuracy at 4 months.⁴⁹

CYP19A1 has also been linked to bone homeostasis in postmenopausal women. One of the major side effects of aromatase inhibitors is bone loss and fractures. Several studies have been conducted examining the relationship between aromatase inhibitors and CYP19A1 and bone homeostasis. One study, involving 286 postmenopausal patients, found that a polymorphism in the 3'-untranslated region of CYP19A1 (1531C>T) was linked to osteoporosis in women >60 years of age. There were 6 other polymorphisms, however, that showed the same association, so the contribution of CYP19A alleles to osteoporosis remains unclear.^{50,51} Another study examining polymorphisms in CYP19A found that postmenopausal women who had a biallelic polymorphism in the 5'-untranslated region of CYP19A1 had decreased spine and hip bone mineral density. This genotype was also associated with a higher prevalence of vertebral

fractures ($P = 0.03$).⁵² Additional studies are needed to help identify which patients may be at higher risk for developing osteoporosis when taking aromatase inhibitors.

Fulverstrant

Fulverstrant is a pure antiestrogen that antagonizes the hormone-dependent activation of ER. It is glucuronidated by UGT1A1, UGT1A3, UGT1A4, and UGT1A8. There is a paucity of data in the literature regarding clinical outcomes associated with UGT polymorphisms and fulverstrant, emphasizing the need for more research in this area.⁵³

Chemotherapeutics

Taxanes

Taxanes stabilize normally dynamic microtubules by binding to sites on tubulin dimers, and its cell cytotoxic effects result from inhibition of cell division. Taxanes, including paclitaxel and docetaxel, are typically used in combination with other chemotherapy agents such as anthracyclines.⁵⁴

Paclitaxel and docetaxel are substrates of P-glycoprotein located in the biliary canalicular membrane. Docetaxel is primarily metabolized by CYP3A4/5, whereas paclitaxel is metabolized by CYP2C8/CYP3A4. Metabolism in both cases results in inactive hydroxylated metabolites.³⁴ Docetaxel and paclitaxel can be bound by a plasma protein known as α 1-acid glycoprotein, which is encoded by the *ORM1* and *ORM2* genes. These genes have been shown to be associated with taxane clearance.⁵⁵ High interpatient variability in *ORM* expression levels have been related to clinical response to taxane.^{56,57} These variations in *ORM* expression levels are most likely due to changes in *ORM* plasma levels in response to inflammation. Various other physiological and pathological states have been suggested as mechanisms of regulation of *ORM* expression.⁵⁸

Related SNPs

CYP1B1

CYP1B1 is the most well-known cytochrome in breast cancer tissue and is usually found in abundance in tumor cells.⁵⁹⁻⁶¹ The CYP1B1*3 polymorphism has been proposed as an indicator for progression-free survival in patients with breast cancer. For example, in a study of 93 patients with breast cancer, Marsh et al⁶² demonstrated an association between CYP1B1*3 and survival in patients with breast cancer. In a study involving 89 patients with breast cancer being treated with paclitaxel and doxorubicin, a 21-gene signature was identified that corresponded significantly

with a complete response.⁶³ The same 21-gene signature corresponded significantly with a complete response in a separate study of 97 patients with breast cancer treated with docetaxel.⁶⁴ This gene signature, known as the Oncotype Dx panel, may help predict response to taxane therapy, potentially allowing the identification of patients who would not benefit from this type of treatment.

Vinorelbine

Vinorelbine is a semisynthetic vinca alkaloid that inhibits DNA replication by disrupting microtubule assembly. It is usually used in advanced breast cancer, especially in patients who have failed anthracycline and taxane therapy.^{5,65} Pharmacogenetic studies of vinorelbine are limited. Metabolism occurs principally by way of CYP3A4, and resistance is believed to be mediated by ABCB1.⁵

Related SNPs

ABCB1 and CYP3A

A polymorphism of ABCB1 (ABCB1 3435C>T) was associated with response to vinorelbine–cisplatin therapy among a group of 69 Han Chinese patients with non-small cell lung cancer.⁶⁶ In a separate study, several CYP polymorphisms, including 2 in CYP3A, were associated with response to vinorelbine-based therapy in a group of 59 Chinese patients with non-small cell lung cancer.⁶⁷ Another study involving mostly Caucasian patients reported no association between polymorphisms in CYP3A or ABCB1 and response to vinorelbine therapy.⁶⁸ These results were confirmed by Schott et al⁶⁹ who showed that in 25 patients with breast cancer; there was no association between CYP3A5 polymorphisms and vinorelbine clearance or toxicity. Additional studies of the PG of vinorelbine in breast cancer therapy are needed.

Cyclophosphamide

Cyclophosphamide is an alkylating agent that is commonly used in combination therapy to treat breast cancer. Cyclophosphamide is metabolized into phosphoramidate mustard and acrolein. Phosphoramidate mustard is an active DNA cross-linking metabolite.⁷⁰ An early study of cyclophosphamide PK in 14 patients with breast cancer reported that there was 54% interindividual variation in central volume of distribution among 14 patients with breast cancer. In the same study, there was 22% interindividual variability in clearance of the cyclophosphamide metabolite 4-O-hydroxycyclophosphamide.⁷¹ It is believed that both body weight and age have an impact on cyclophosphamide PK, with younger patients having a faster cyclophosphamide half-life.^{72,73} The PG of cyclophosphamide

have not been studied extensively because it is commonly used in combination with other chemotherapeutic agents.⁷⁴

Related SNPs

CYP3A

A recent prospective cohort study was performed including 127 patients with premenopausal early-stage breast cancer. The purpose of the study was to determine whether there was an association between polymorphisms of cyclophosphamide metabolizing enzymes and risk of ovarian failure after adjuvant chemotherapy. Patients who were less than 45 years of age and carried the CYP3A4*1B allele had a significantly longer time to reach chemotherapy-related ovarian failure.⁷⁵ In another study involving 85 patients with breast cancer, the CYP3A4*1B or CYP3A5*1 polymorphism was associated with survival and increased cyclophosphamide plasma area under the time curve, which is an indicator of poor metabolism.⁷⁶

CYP2B6

CYP2B6 is involved in the activation of cyclophosphamide.⁷⁷ The CYP2B6*6 polymorphism was linked to higher clearance and shorter cyclophosphamide half-life in a study of 103 Japanese patients with cancer (lymphoma or breast cancer). Other polymorphisms of CYP2B6 (–2320C>T; –705T>C; 18492C>T) were associated with leucopenia. However, in this same study, there was no association between cyclophosphamide PK and CYP3A polymorphisms.⁷⁸ These results were corroborated by a recent study in 124 Caucasians, which demonstrated no association between CYP3A or CYP2B6 polymorphisms and cyclophosphamide PK.⁷⁹ The Petros Study also failed to demonstrate an association with CYP2B6 polymorphisms.⁷⁶ Additional studies are needed to better understand the link between CYP2B6 polymorphisms and response to cyclophosphamide therapy.

Gemcitabine

Gemcitabine is a nucleoside analog that is transported into cells by the transporters SLC28 and SLC29. It is then converted by deoxycytidine kinase (DCK) into the active metabolites gemcitabine diphosphate and gemcitabine triphosphate. Gemcitabine diphosphate inhibits thymidylate ribonucleotide reductases (RRM1 and RRM2), which generate the nucleotides required for DNA synthesis and repair. The decrease in available nucleotides results in the incorporation of gemcitabine triphosphate into the DNA, resulting in strong inhibition of DNA synthesis and repair.^{80,81}

Cytidine deaminase

Gemcitabine is inactivated by cytidine deaminase (CDA). In a study involving 256 Asian patients with cancer, the nonsynonymous CDA A70T polymorphism was associated with reduced gemcitabine clearance and increased incidence of severe neutropenia in patients taking a combination of gemcitabine with cisplatin, carboplatin, or 5-fluorouracil (5-FU).⁸² This particular CDA variant is more common in Africans than in Japanese or Europeans (13% vs 4.3% vs 0%).⁸³

RRM1

Variants in RRM1 (2455A>G and 2464G>A) have been associated with a significant reduction in incidence of neutropenia in patients receiving gemcitabine alone. RRM1 polymorphisms have also been linked to decreased use of granulocyte colony-stimulating factor and poorer progression-free survival and overall survival outcomes.⁸⁴ A retrospective study of patients with advanced stage breast cancer who were being treated with gemcitabine/carboplatin found that the -37C and -524T RRM1 polymorphisms were associated with better tumor response, progression-free survival, and overall survival.⁸⁵

Deoxycytidine kinase (DCK)

Variants in DCK, the rate-limiting activating enzyme in the gemcitabine pathway, have been identified, but further studies are needed to determine the relationship between these variations and response to gemcitabine in patients with breast cancer.⁸⁶

Capecitabine/5-FU

Capecitabine is an oral prodrug of fluorouracil (5-FU). Variations in thymidylate synthetase (TS), the principal target of 5-FU, methylenetetrahydrofolate reductase (MTHFR), a key regulatory enzyme in folate metabolism, and dihydropyrimidine dehydrogenase, which catabolizes 5-FU, might potentially contribute to interindividual variability in patient responses to 5-FU-based therapeutic management.⁸⁷

Related SNPs

MTHFR and TS

Two common polymorphisms of MTHFR, C677T and A1298C, result in decreased enzyme activity and chemosensitivity of tumor cells. In a study of 248 African-American and Caucasian patients with breast cancer, the presence of a 1298 variant (A/C or C/C) was associated with decreased survival rate. The opposite effect was observed in patients with variant alleles at codon 677 (C/T or T/T); however, this result was not statistically

significant. In addition, the authors noted that these results were affected by race and ethnicity.⁸⁸ A separate study including 1,067 Asian patients with breast cancer found that MTHFR 677C>T was associated with increased risk of death.⁸⁹

Variable copy number of a 28-basepair tandem repeated sequence (TSER*2, TSER*3, TSER*4, TSER*, and TSER*9) in the TS enhancer region has been associated with increased TS expression and significantly poorer response to treatment.⁵ TSER*2 and TSER*3 are the predominant alleles in most populations.⁹⁰ The TS TSER polymorphism was associated with survival in a small population of patients with breast cancer (35 patient's total). In contrast, a larger study of 93 patients receiving 5-FU and methotrexate found no association between MTHFR or TS polymorphisms and breast cancer outcomes.⁹¹

CES2

Carboxylesterase 2 is one of the 3 enzymes responsible for converting capecitabine to 5-FU. In a study of 135 patients with breast cancer, the CES2-832C>G polymorphism was associated with a significantly enhanced response to capecitabine. It was also associated with an increased time to progression as compared with patients with wild-type CES2.⁹²

Dihydropyrimidine dehydrogenase (DPYD)

Complete or partial DPYD deficiency results in severe 5-FU toxicity in approximately 3%–5% of individuals. Although at least 20 functional DPYD variants have been described, the DPYD*2A splice site variant is assumed to be the most common.^{6,93}

Platinum

Platinum induces interstrand DNA cross-linking, leading to the cessation of DNA synthesis, cellular apoptosis, and toxicity. Platinum is modulated by proteins involved in DNA repair (ERCC1, ERCC2, and XRCC1), DNA detoxification (GSTP1 and MPO), and DNA transport (SLC31A1, ABCC2, and ABCG2).^{5,6,93}

To date, no genetic polymorphisms that specifically affect platinum metabolism or response have been identified. In a randomized trial of carboplatin and a taxane in patients with ovarian cancer, genetic polymorphisms in proteins of the platinum pathway (ABCC2, ABCG2, ERCC1, ERCC2, GSTP1, MPO, and XRCC1) were not significantly associated with clinical outcomes or toxicity.^{5,6,62} Moreover, most studies related to platinum pharmacogenetics have been performed on patients with non-small cell lung cancer.

Related SNPs

GSTM1 and MET1F

A recent study of 85 patients with breast cancer being treated with a combination of cisplatin, cyclophosphamide, and carmustine demonstrated that patients with a gene deletion of *GSTM1* had an increased median survival time. However, it was not possible to determine whether the effect was related to cisplatin, carmustine, or both. Patients who carried the MET1F G-7T polymorphism had a lower concentration of platinum 72 hours after administration and shorter survival.⁷⁶

ERCC1

As noted earlier, most studies of polymorphisms related to platinum therapy have been performed in patients with non-small cell lung cancer, a few of which are worth mentioning here due to their potential relevance to breast cancer. In a study of 62 patients with non-small cell lung cancer that were being treated with docetaxel and cisplatin, there was an association between the synonymous N118N polymorphism in ERCC1 and median survival time and time to progression.⁹⁴ Similar results were found in another study involving 109 patients that were treated with cisplatin combination therapy, in which the ERCC1 N118N was significantly associated with overall survival. However, no association between ERCC1 N118N and ERCC2 polymorphisms were demonstrated in 8 separate studies, one of which involved 65 patients receiving gemcitabine and cisplatin therapy.^{63,95} Thus, the relationship between ERCC polymorphisms and response to cisplatin remains uncertain.

Anthracyclines

The anthracyclines, which include doxorubicin and epirubicin, exhibit extremely variable PK among patients. This may be due to the fact that anthracyclines interact with a complex array of pathways involving various metabolizing enzymes and transporters.⁵

Carbonyl reductases (CBR1, CBR3) and aldo-ketoreductases (AKR1A1, AKR1C2) are responsible for converting doxorubicin and epirubicin via phase 2 reduction reactions to doxorubicinol and epirubicinol, respectively, which are then inactivated by CYP3A4 and CYP3A5. Efflux is mediated by ABCB1, ABCC1, ABCC2, and ABCG2 transporters.⁵ Epirubicin also undergoes phase 2 reactions by conjugation, mostly via UGT2B7. Orphan nuclear receptors are involved in regulating the transcription of many of the CYP enzymes and transporters of the anthracycline pathway and may contribute as well to variability.^{5,53} *ABCB1*, which encodes P-glycoprotein, a well-known ATP-binding cassette

transporter, has been associated with drug resistance. The most common ABCB1 SNPs are 1236C>T, 2677G>T/A, and 3435C>T, which appear to disrupt ABCB1 substrate transport.⁵

Several genes have been identified that may be involved in anthracycline-mediated killing of tumor cells. For instance, glutathione s-transferases (GSTs) are involved in the catalysis of secondary organic oxidation products formed by chemotherapy. These products can cause additional cellular injury; thus, individuals who lack GST may have better responses to anthracyclines.⁵

The anthracyclines have been used for many years; however, the genetic basis of interpatient variability remains unclear. Large, prospective clinical studies are needed to determine the genetic predictors that may contribute to variations in anthracycline response.⁵

Related SNPs

CBR1 and CBR3

CBR1 and CBR3 function as phase 1 metabolizers of doxorubicin. Doxorubicin is metabolized to the inactive metabolite doxorubicinol, which has been implicated in doxorubicin cardiotoxicity. Recently, the CBR3 11G>A polymorphism was linked to increased tumor reduction and hematologic toxicity in 101 southwest Asian patients with breast cancer. CBR3 11G>A is associated with decreased conversion of doxorubicin to doxorubicinol, whereas CBR3 730G>A is associated with increased conversion of doxorubicin to doxorubicinol.⁹⁶

ABCB1 and ABCG2

The ATP-binding cassette transporters ABCB1 and ABCG2 have been well characterized in terms of polymorphisms and doxorubicin PK. Although no association has been documented between ABCG2 421C>A and doxorubicin PK, 3 common ABCB1 polymorphisms, 1236C>T, 2677G>A/T, 3435C>T, were associated with doxorubicin clearance in a recent study of 62 Asian patients with breast cancer.⁹⁷ Another study examining 68 patients being treated with anthracycline or combination anthracycline/taxane therapy also found an association between the 3435T variant and better clinical response.⁹⁸ A more recent study of 41 Brazilian women, however, failed to demonstrate a similar link.⁹⁹

SLC22A16

SLC22A16 is an anthracycline influx transporter. In a study of 62 Asian patients with breast cancer, a SLC22A16 poly-

morphism, 146A>G, was linked to increased exposure to doxorubicin and doxorubicinol. The clinical impact of this finding as it relates to doxorubicin response and toxicity was not determined, and remains to be elucidated.⁹⁷

It is important to note that most of the studies mentioned above were carried out in Asian populations. Therefore, the PG of anthracycline response in non-Asian populations is unclear. It is also important to note that there are significant variations in allele frequencies among various populations. For instance, SLC22A16 146A>G occurs at a much higher frequency in Asian populations (13%–18%) as compared to Caucasians (9%).^{100,101} These types of variations need to be considered when validating PG approaches in different populations.

UGT2B7

UGT2B7 is the enzyme responsible for glucuronidation of epirubicin. Polymorphisms of UGT2B7 have been identified, but do not appear to be associated with any changes in rate of glucuronidation of epirubicin.¹⁰²

NQO1

The NQO1 556C>T and the NQO1*2 alleles have been shown to predict survival outcomes in patients with breast cancer and also predict response to epirubicin in breast carcinoma cells *in vitro*.¹⁰³ A more recent study, however, failed to corroborate these results,¹⁰⁴ leaving the role of these variations in question.

Targeted therapy

Trastuzumab/lapatinib/bevacizumab

Targeted therapeutics, including anti-HER2 antibodies (trastuzumab and lapatinib) and bevacizumab, an antiangiogenic agent directed against vascular endothelial growth factor (VEGF), are approved treatments for advanced breast cancers and are currently in clinical trials for early-stage breast cancer. Although both trastuzumab and lapatinib inhibit the same receptor, ErbB2, using the 2 drugs in combination is a potentially attractive option because each agent targets a different part of the receptor; trastuzumab targets the extracellular domain, and lapatinib targets the intracellular domain. In addition, the drugs appear to have different mechanisms of action; trastuzumab increases internalization and degradation of ErbB2, whereas lapatinib inhibits ErbB2 tyrosine kinase activity.¹⁰⁵

The majority of breast cancers are responsive to estrogen, but upon progression of the disease, other growth-promoting pathways are activated, including the ErbB receptor signaling

system. The ErbB/HER family of epithelial growth factor receptors (EGFRs) is composed of 4 members that share a high degree of sequence homology: EGFR (ErbB1, HER1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER 4).^{106,107} The prototypical member of this family, EGFR, is a transmembrane protein consisting of an extracellular binding domain, a hydrophobic transmembrane domain, and a cytoplasmic tyrosine kinase domain.¹⁰⁵ ErbB2 is commonly overexpressed in breast cancer cells. It is this overexpressed ErbB2 that is the major target for both trastuzumab and lapatinib.¹⁰⁸ The binding of trastuzumab to its target on the extracellular domain of ErbB2 may be affected by differential amino acid expression and functional polymorphisms in this region of the receptor and may influence individual drug responses.¹ It has also been suggested that lapatinib PK may be altered in individuals carrying polymorphisms in the gene coding for hepatic CYP2C19 or P-glycoprotein.¹⁰⁸

Related SNPs

Fc- γ receptor

In 2008, Musolino et al¹⁰⁹ investigated Fc- γ receptor polymorphisms and their association with the clinical efficacy of trastuzumab-based therapy for HER2-positive (HER+) patients with breast cancer. Fc- γ polymorphisms have been shown to affect antibody-dependent cell-mediated cytotoxicity responses of natural killer cells and monocytes. The investigators identified 2 polymorphisms, Fc- γ RIIIA-158 V/V and Fc- γ RIIa-131 H/H that were significantly associated with objective response rate and progression-free survival. The H/H and V/V genotypes were also associated with higher trastuzumab-mediated cytotoxicity in peripheral blood mononuclear cells as compared with other genotypes. These results underscore the need for additional studies of the role of Fc- γ receptor polymorphisms on clinical outcomes with trastuzumab therapy.¹⁰⁸

Future applications of PG

The US Food and Drug Administration (FDA) recently approved a DNA microarray-based pharmacogenetics test for CYP2D6 polymorphisms (AmpliChip CYP450 test). This test can detect 27 different CYP2D6 variants, including non-functional variants (CYP2D6*3, CYP2D6*4, CYP2D6*5, and CYP2D6*6), deficient variants commonly found in Asians and black Africans (CYP2D6*10 and CYP2D6*17), and ultra-rapid variants found in Middle Easterners and Ethiopians (CYP2D6*2XN).¹⁰⁹ A label change has been proposed to introduce the possibility of testing for CYP2D6 polymorphisms prior to tamoxifen use due to the known

increase in breast cancer recurrence in women with altered CYP2D6 metabolism.⁷⁶ A final decision about testing is forthcoming.⁹²

There is a prevalent belief among researchers and clinicians that PG approaches to cancer therapy (ie, personalized medicine) will be cost prohibitive, due to the current pharmaceutical blockbuster model, government regulation, a dysfunctional payment system, and physician behaviors.¹¹⁰ Studies that analyze the pharmacoeconomics of personalized medicine, including the cost effectiveness of using genetic information to inform drug choice and therapy regime, are strongly recommended. In addition, effective implementation of PG in the clinical setting will require active involvement of the FDA, including establishment of protocols or guidelines on how genetic information collected from the population should be handled or used. The gene signature of individual tumors might predict utility of specific treatment regimens in individual patients with breast cancer.¹¹¹

Ethics of PG

The fact that PG requires the collection of specific genetic information, and in some cases, the sequence of the patient's complete genome, raises the question of who should have access to this information and how the use of this data should be regulated.¹¹²⁻¹¹⁵ In situations where a subject's genetic information has been collected as part of a clinical diagnosis, the individual may have a strong interest in keeping the information confidential, even though others may believe that they have a claim to the information. For example, family members who are genetically related may want to know the results of genetic studies. Third-party health insurance providers may claim to have a right to the information if they are to accurately assess the risk they are taking on by insuring the patient. Employers may wish to have access to the information as well since they will bear the majority of the cost of insuring the individual. It has been speculated that the reluctance of individuals to undergo certain forms of genetic testing today is driven by a fear of losing their job, their health insurance, or both. In other words, people believe that by submitting to such tests, they in essence give up certain rights.^{112,113}

Another ethical issue involved in PG is cost.¹¹⁶ A point of general consensus within the pharmaceutical sector is that the cost of genetically tailored drugs is likely to be high. This is because major research must be carried out to identify the genetic profiles that will make personalized medicine possible, followed by expensive and time-consuming research

to test existing and novel drugs in the context of particular genetic profiles. Given that these costly therapies, should they emerge, might be accessible to only a limited segment of the general population, it remains unclear whether pharmaceutical companies would be willing to invest in such research. There is the possibility that because of the potentially small financial gain from this novel approach to medicine, pharmaceutical companies will be less inclined to engage in the effort to make personalized medicine a reality.¹¹⁷

Subjects who are pharmacogenomically classified as nonresponsive to drug treatment may carry with them a stigma of rejection, particularly by private insurance companies. This may bring about a personal economic crisis and could also result in psychological issues for people or communities as the idea of being "untreatable" becomes more widespread.

Finally, as mentioned above, it is widely expected that PG therapies will be more expensive than current regimes, and the resulting premium drug prices may make these new therapies inaccessible to those who are struggling economically. Additional questions, such as will insurance companies pay for more expensive PG therapies or for the tests needed to prescribe them, and if so, will the benefits of PG be available only to those who are able to pay for them "out-of-pocket," must be addressed as PG becomes more commonplace in the clinical setting. A very important act for future progress in that regard is the Nondiscrimination Act (GINA) passed by the congress in 2008 to minimize the risk of exploitation by insurers and other interested parties of personal genetic data.

Conclusion

PG is a discipline that is rapidly moving beyond the study of a single gene, to a comprehensive analysis of entire pathways that integrates aspects of PK and PD studies. The possibility of therapy-based knowledge of how the patient will best respond will soon be possible through the clinical application of PG. However, in order to reach this goal of individualized intervention, clinical and epidemiologic studies are urgently needed to assess (1) how drug response varies among individuals with different genotypes, (2) the prevalence of relevant genotypes in the population and in specific subpopulations, and (3) the degree to which environmental factors (such as other drugs and diet) interact with genetic factors to influence drug response. Both clinical trials and observational epidemiologic studies are

crucial for generating the population-based data needed to apply PG to the practice of medicine and public health in the 21st century. The promise of PG studies is dramatic improvements in drug safety and efficacy, thereby transforming patient care from a one-drug-fits-all approach into customized therapy.

Disclosure

The authors report no conflicts of interest in this work.

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