Primer on Medical Genomics
Part XII: Pharmacogenomics—General Principles With Cancer as a Model
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The Human Genome Project has resulted in a new era in the field of pharmacogenetics in which researchers are rapidly discovering new genetic variation, which may help to explain interindividual variability in drug efficacy and toxicity. Pharmacogenetics is the study of the role of genetic inheritance in individual variation in drug response and toxicity. With the convergence of advances in pharmacogenetics and human genomics, the field of pharmacogenomics has emerged during the past decade. Pharmacogenomics is used to refer to the study of the relationship between specific DNA-sequence variation and drug effect. In few other disciplines of medicine are the clinical examples of pharmacogenetics more striking than in oncology. In this field, treatment of patients with cancer is accomplished primarily through the use of chemotherapeutic drugs that have narrow therapeutic indexes, ie, the difference between the toxic and therapeutic dose is relatively small. In this review, we discuss several selected, clinically relevant examples of ways in which sequence variation in genes that encode drug enzymes, transporters, and drug targets can alter the efficacy and/or adverse-effect profile of “standard” doses of chemotherapeutic drugs. Additionally, we discuss some of the ways in which physicians are currently applying this knowledge in the treatment of patients with cancer.


Although many clinical variables can contribute to variation in drug response (age, sex, diet, organ function), genetic variation in the genes that influence drug disposition and drug targets is recognized increasingly as one of the principal variables that can influence drug effect. The concepts that underlie pharmacogenetics originated many years ago from the clinical observation that administration of succinylcholine.1 Later, researchers discovered that the DNA sequence variation within the gene that encodes for butyrylcholinesterase could significantly alter the clearance of succinylcholine, leading to the clinical observation of prolonged apnea.2

Although drug effect is a complex phenotype that encompasses many factors, those early and often dramatic examples facilitated acceptance of the fact that inheritance could be an important factor influencing drug effect. Today, that original bedside to bench flow of pharmacogenetic information (the so-called phenotype to genotype approach) is being supplemented by a systematic search for functionally significant DNA sequence variation within genes of importance for drug effect. Much of this genetic variation is in the form of single nucleotide polymorphisms (defined as variants with frequencies of ≥1%), which can alter the amino acid sequence of the encoded protein, alter RNA splicing, or alter transcription. After the identification of specific DNA sequence variants, investigators are able to establish quickly in vitro whether that variation results in a functional change in phenotype (eg, altered expression of RNA and/or change in protein levels). This

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resultant wave of bench to bedside data is helping to transform pharmacogenetics into pharmacogenomics and has supplemented the more “traditional” paradigm of phenotype to genotype discovery to include a genotype to phenotype approach. Recently, it became clear that the evaluation and correlation of haplotypes (combination of polymorphisms on one strand of DNA that are inherited together) can often result in better correlation with phenotypes than with individual polymorphisms. Unfortunately, no good assay to determine haplotype unequivocally is yet available for widespread use, thus limiting the implementation of haplotype data into translational studies. Most often, haplotypes must be “inferred” computationally.

In few other disciplines of medicine are the concepts of pharmacogenetics better illustrated and the promise of pharmacogenomics more apparent than in the treatment of cancer. Administration of “standard” doses of chemotherapy to patients with inherited deficiencies in enzymes responsible for their metabolism and disposition can result in marked toxicity, which at times can be lethal. Conversely, patients who have increased enzymatic activity may be at risk for treatment failure, a tragedy when dealing with a potentially fatal illness. The traditional method by which individualized anticancer drug doses are developed and determined has involved the use of body surface area measurements and weight-based dosing. However, multiple studies have indicated that dosing in this manner does not reliably account for the variability in clearance of most chemotherapeutic drugs. Recently, several excellent review articles were published regarding the general principles of pharmacogenetics and cancer pharmacogenetics. In this review, we focus on several selected, clinically relevant examples in which variation in genes encoding proteins that influence drug metabolism, drug transport, and drug targets can alter both the toxicity and the effectiveness of some commonly used chemotherapeutic drugs.

THIOPURINES
The thiopurine drugs mercaptopurine and azathioprine, a prodrug that is converted to mercaptopurine in vivo, are purine antimetabolites used clinically to treat both pediatric and adult leukemias and as immunosuppressant agents. Thiopurines are metabolized in part by S-methylation catalyzed by the enzyme thiopurine S-methyltransferase (TPMT). More than 20 years ago, it was reported that Caucasian populations can be separated into 3 groups on the basis of the level of TPMT activity in their red blood cells and other tissues and that the level of activity is inherited in an autosomal codominant fashion (Figure 1, A). Subsequently, investigators showed that individuals who received standard doses of thiopurines and who were homozygous for extremely low levels of TPMT activity or for no activity (Figure 1, A) had substantially elevated concentrations of active drug metabolites (6-thioguanine nucleotides) and a markedly increased risk of life-threatening drug-induced myelosuppression. As a result, the phenotypic test for the level of TPMT activity in red blood cells and subsequently DNA-based tests were among the first pharmacogenetic tests to be used in clinical practice. Patients with inherited low levels of TPMT activity can be treated with thiopurine drugs, but the dose must be reduced substantially to avoid toxicity.

The TPMT gene has been cloned, and the most common variant allele responsible for low levels of activity among Caucasian populations encodes a protein with 2 alterations in the amino acid sequence as a result of single nucleotide polymorphisms (Figure 1, B). These sequence changes result in a striking reduction in the quantity of TPMT, at least in part because the variant protein is degraded rapidly. A series of less frequent TPMT variant alleles has also been described. Large differences exist in the types and frequencies of TPMT alleles among ethnic groups. TPMT*5A, the most common allele responsible for extremely low levels of enzyme activity in Caucasians (Figure 1, B), has not been observed in China, Korea, or Japan. In summary, TPMT represents an example of the individualization of therapy based on pharmacogenetic data. The clinical implications of the polymorphisms are so striking that a Food and Drug Administration Advisory Committee recently recommended revision of thiopurine labeling to include information on this genetic polymorphism for drug metabolism.

5-FLUOROURACIL
5-Fluorouracil (5-FU) and the oral prodrug capecitabine are among the most commonly prescribed anticancer agents. 5-Fluorouracil is an excellent example of the way in which genetic variation in both a drug-metabolizing enzyme (dihydropyrimidine dehydrogenase [DPD]) and a drug target (thymidylate synthase [TS]) can influence both toxicity and response to treatment.

Dihydropyrimidine dehydrogenase is the initial and rate-limiting enzyme in the catabolism of the pyrimidine bases uracil and thymine, and it also catalyzes the reduction of 5-FU to the inactive metabolite dihydofluorouracil (Figure 2). In humans, up to 85% of an administered dose of 5-FU is degraded by DPD. The importance of DPD in 5-FU toxicity has been illustrated by the clinical course of patients with inherited DPD enzyme deficiency who are treated with this drug. After administration of standard doses of 5-FU, such patients experience profound toxic effects including potentially life-threatening gastrointestinal toxicity, myelosuppression, and neurologic toxicity, which can include peripheral neuropathy, encephalopathy,
and demyelination.\textsuperscript{20-27} Thus far, more than 30 mutations in the \textit{DPD} gene have been described, at least 20 of which have been reported to be functional.\textsuperscript{28,29} Analysis of the prevalence of the various \textit{DPD} genetic variants among \textit{DPD}-deficient patients has shown that a splice-site polymorphism, IVS14+1G>A (ie, a G to A alteration in the nucleotide at the intron 14 acceptor splice site), is the most common (52%).\textsuperscript{30} The allele frequency of the IVS14+1G>A polymorphism in Caucasian populations is reported to be 0.9%,\textsuperscript{25} but this polymorphism has not been observed in Japanese, Taiwanese, or African American populations, further emphasizing the possibility of striking ethnic variation in variant allele type and frequency.\textsuperscript{31}

The routine application of \textit{DPD} pharmacogenetic information to clinical practice has yet to be achieved. To date, the most reliable method for determining phenotype, measurement of \textit{DPD} activity, uses a radioassay for \textit{DPD} activity in human peripheral lymphocytes.\textsuperscript{31,32} Unfortunately, this enzyme assay is complicated and not widely available as a screening test.\textsuperscript{31-34} Another recently reported means for assessing \textit{DPD} phenotype, the uracil breath test, uses oral administration of 2-\textsuperscript{13}C-uracil, resulting in the release of the 2-carbon of uracil as \textsuperscript{13}CO\textsubscript{2} in the presence of active \textit{DPD}.\textsuperscript{35} In a small study consisting of several \textit{DPD}-deficient patients, Mattison et al\textsuperscript{35} showed that the uracil breath profiles correlated significantly with level of enzyme activity.

With the identification of a series of mutations responsible for \textit{DPD} deficiency, some researchers have advocated screening patients for the IVS14+1G>A polymorphism, potentially the most important \textit{DPD} polymorphism in Caucasian populations.\textsuperscript{25,35} In a retrospective study, this \textit{DPD} polymorphism accounted for nearly 28% of a group of patients.
patients with severe 5-FU toxicity and nearly half of those partially or completely deficient in DPD. However, in a study of more than 650 patients treated prospectively with 5-FU, among 85 patients with 5-FU-related World Health Organization grade 3 or 4 toxicity, only 4 patients carried the splice junction polymorphism. Thus, only 5% of severe toxicity related to 5-FU use could be explained by the most common DPD variant.

Because of the large number of sequence variations and because studies to date have shown an inconsistent correlation between DPD genotype and phenotype, Ezzeldin et al hypothesized that DPD-deficient patients with compound heterozygote genotypes may be responsible for some of the previous conflicting reports that suggested a lack of correlation between phenotype and genotype. However, with the ability to test for multiple mutations, future studies will likely show a more accurate assessment of DPD phenotype through the study and correlation of individual DPD haplotypes.

THYMIDYLATED SYNTHASE

5-Fluorouracil is a prodrug that requires activation to 5-fluoro-2-deoxyuridine monophosphate (5-FdUMP) for its cytotoxic effects. That cytotoxicity is mediated primarily by the inhibition of TS, which requires the formation of a ternary complex consisting of 5-FdUMP, TS, and 5,10-methylene tetrahydrofolate (Figure 2). A polymorphism within the 5′-promoter enhancer region, the so-called TSER of the TS gene, consisting of tandem repeats of 28 base pairs, has been implicated in modulating tumor TS messenger RNA and protein levels and in the clinical outcome after the administration of fluoropyrimidines. The vast majority of Caucasian subjects carry either a double (TSER*2) or a triple (TSER*3) repeat for this polymorphism, although 4, 5, and 9 copies of the repeated sequence have been described. Allele frequencies in Southwest Asian subjects are similar to those found in Europeans. However, the homozygous triple repeat is almost twice as common in Chinese subjects (67%) as in Caucasian subjects (38%). Patients homozygous for the TSER*3 genotype have elevated intratumoral TS messenger RNA levels, elevated TS protein levels, and poorer response rates after 5-FU chemotherapy compared with TSER*2 homozygotes. With the introduction of both oxaliplatin and irinotecan (CPT-11) in the treatment of colorectal cancer, 5-FU is now most commonly administered in combination with either CPT-11 and/or oxaliplatin. Recent data from a large North Central Cancer Treatment Group prospective phase 3 study (N9741) in which patients with metastatic colorectal cancer received 5-FU-based chemotherapy (either with CPT-11 or oxaliplatin) showed no differences in clinical response (response rates or time to progression) based on the presence of the TSER*3 genotype. In this multidrug therapy setting, it is possible that the effect of the TS polymorphism is not as important in determining outcome as has been reported when 5-FU is used alone.

URIDINE DIPHOSPHATE GLUCURONOSYLTRANSFERASE 1A1 AND IRINOTECAN

Irinotecan (CPT-11) is a topoisomerase I inhibitor approved for use as first-line therapy for metastatic colorectal cancer in combination with 5-FU. CPT-11 is metabolized in vivo to 7-ethyl-10-hydroxy camptothecin, SN-38 (Figure 3), which is 1000 times more potent of an inhibitor of topoisomerase I than is the parent drug. In humans, both gastrointestinal (diarrhea) and hematologic (neutropenia) toxic effects are dose limiting after administration of CPT-11. Recently, an independent panel found that patients treated in 2 large randomized trials with CPT-11 plus bolus fluorouracil had a 3-fold higher rate of treatment-induced or treatment-exacerbated death than did patients treated on the other arms of the respective studies. Most of these deaths were due to a constellation of gastrointestinal symptoms, including diarrhea, nausea, vomiting, anorexia, and abdominal cramping. These symptoms were often associated with severe dehydration, neutropenia, fever, and electrolyte abnormalities. Grothey et al reported similar findings of an unexpectedly high rate of deaths due to dehydration, neutropenia, and sepsis in patients receiving the combination of CPT-11 and capecitabine.

The results of these and other trials of CPT-11 have led investigators to study whether genetic variation in the genes whose protein products are responsible for CPT-11 metabolism account for some of the differences seen in the
rates of diarrhea and myelosuppression. SN-38 is inactivated by glucuronidation to form the glucuronide conjugate (SN-38G) in a reaction catalyzed by the polymorphic hepatic enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), forming the inactive metabolite SN-38 glucuronide (SN-38G), which is eliminated in the bile. APC = aminopentane carboxylic acid; NPC = 7-ethyl-20-(4-amino-1-piperidino) carbonyloxycamptothecine.

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A dinucleotide repeat polymorphism in the TATA box in the promoter for UGT1A1 results in reduced hepatic UGT1A1 expression and is thought to be the most common cause of Gilbert syndrome (mild unconjugated hyperbilirubinemia). 59-61 Specifically, human liver samples either heterozygous or homozygous for 7 TA repeats (UGT1A*28 allele) have decreased UGT1A1 expression and reduced SN-38 glucuronidation compared with samples homozygous for the most common allele (6 TA repeats). 62 The frequencies of these polymorphic alleles, like those for TPMT and DPD, vary considerably among different ethnic groups, with the 7 repeat allele varying from a frequency of 16% in Chinese subjects to nearly 40% in Europeans and East Indians. 61-63

Recent studies showed the effect of the UGT1A1*28 polymorphism on CPT-11–induced toxicity. In a retrospective study of patients treated with CPT-11, those who carried the UGT1A1*28 polymorphism had a 7-fold increased risk for severe toxicity (leukopenia/diarrhea) compared with patients without the UGT1A1*28 polymorphism. 64 In a prospective phase 1 pharmacogenetic study of single-agent CPT-11 administered every 3 weeks, patients who carried the UGT1A1*28 polymorphism had significantly lower SN-38 glucuronidation rates than those without the UGT1A1*28 polymorphism. 65 Furthermore, severe (grade 3 or 4) diarrhea or neutropenia was seen only in patients with the UGT1A1*28 polymorphism. Recent pharmacogenetic data from the North Central Cancer Treatment Group N9741 study showed that patients receiving CPT-11–based chemotherapy who were homozygous for the most common allele (6 TA repeats) had significantly lower rates of either grade 4 or grade 5 neutropenia than those who carried the UGT1A1*28 polymorphism. 51 Although only 8.6% of patients with the UGT1A1 6/6 genotype had either grade 4 or grade 5 neutropenia, nearly 36% of patients with the 7/7 genotype had either grade 4 or grade 5 neutropenia. Furthermore, a trend toward differences in response rates was shown on the basis of the status of the UGT1A1*28 polymorphism.

Although the importance of UGT1A1 pharmacogenetics in mediating CPT-11–related toxicity has been shown clearly, clinical guidelines have yet to be developed that direct oncologists how to use UGT1A1 genotyping information in the prospective management of patients receiving CPT-11–based therapy. Currently at the Mayo Clinic, we are prospectively evaluating the impact of the UGT1A1*28 polymorphism in a phase 1 study of the combination of CPT-11, capecitabine, and oxaliplatin. Patients at highest risk for CPT-11–related toxicity (either heterozygous or homozygous for UGT1A1*28) are being enrolled first to determine the safest dose of CPT-11 that can be administered in combination with capecitabine and oxaliplatin. After this determination, patients who do not carry the UGT1A1*28 polymorphism will be enrolled, and the dose of CPT-11 will be escalated to determine whether patients who do not carry the UGT1A1*28 genotype can tolerate higher doses of CPT-11 in combination with capecitabine and oxaliplatin than those who do carry this variant allele.

PLATINUM CHEMOTHERAPY

The platinum analogues (cisplatin, carboplatin, and oxaliplatin) are widely used in the treatment of a variety of solid tumors, including testicular, lung, ovarian, breast, and gastrointestinal cancers. A large body of evidence suggests that the success of platinum complexes in killing tumor cells results mainly from their ability to form various types of DNA adducts. 66 The nucleotide excision repair pathway, which is involved in the repair of bulky DNA lesions such as pyrimidine dimers, other photo-products, larger chemical adducts, and cross-links, 67 includes several well-defined genes such as excision repair cross-complementation group 1 and xeroderma pigmentosum group D (ERCC1 and XPD) that encode proteins involved in the removal of cisplatin-DNA adducts. Recent studies indicated that genetic variation in the genes whose protein products are involved in nucleotide excision repair pathway (eg, XPD and ERCC1) as well as genes encoding proteins in other DNA repair pathways x-ray cross-complementing (XRCC1) may influence response to platinum chemotherapy.

The XPD helicase, a component of the TFIIH transcription factor complex, participates in DNA unwinding to allow gene transcription by RNA polymerase II and/or the removal of DNA lesions induced by platinum chemotherapy. 68 Although rare XPD mutations that result in the
clinical syndrome of xeroderma pigmentosum are well described, the effects of common polymorphisms in this gene (C156A, Asp312Asn, and Lys751Gln) on DNA repair capacity are less clear.

The XRCC1 protein plays an important role in base excision repair. The enzyme encoded by this gene temporarily binds to single-strand interruptions in DNA and may act to recruit repair proteins. A polymorphism within codon 399 of the XRCC1 gene (Arg399Gln) is known to result in decreased DNA repair.

Recently, several studies suggested that common variants within the XPD and/or XRCC1 genes may predict clinical outcome after the administration of platinum-based chemotherapy. In a retrospective study in which patients with colorectal cancer received oxaliplatin plus 5-FU, those who carried the XPD Lys751Gln polymorphism (either heterozygous or homozygous) had significantly decreased response rates and survival compared with those homozygous for the Lys751/Lys751 genotype.

Data derived from this same cohort of patients also suggested the potential for a relationship between the XRCC1 (Arg399Gln) polymorphism and clinical outcome. A higher percentage of patients with the Arg/Arg genotype responded to therapy, whereas the presence of a variant allele (either Gln/Gln or Gln/Arg genotype) was seen more commonly in the nonresponders.

We recently presented the results of a prospective phase 2 study that examined the impact of the common XPD (C156A, Asp312Asn, and Lys751Gln) and XRCC1 (Arg399Gln) polymorphisms in women receiving docetaxel and carboplatin as first-line treatment for metastatic breast cancer. We found that patients with the XPD 312 Asp/Asp genotype (wild type) had lower response rates (50%) and clinical benefit (50%) (defined as no evidence of progression for at least 6 months) than did patients with one Asn allele (response rate of 56% and clinical benefit rate of 67%). Patients homozygous for the XPD 312 Asn/Asn genotype had the highest response and clinical benefit rate (88%; P=.07 for trend). No correlation with either response rates or clinical benefit was seen with the XRCC1 Arg399Gln polymorphism.

Recent in vitro functional genomic studies have attempted to explain the functional importance of XPD polymorphic variants. Lymphoblastoid cell lines, after ultraviolet (UV) light exposure, showed similar rates of apoptosis for those homozygous or heterozygous for Asp at codon 312, whereas cell lines homozygous for Asn showed a 2-fold increase in apoptosis rate response to UV light. The presence of Lys or Gln at codon 751 did not influence the apoptotic response to UV light. However, other studies have shown a positive correlation between the Lys751Gln polymorphism and DNA repair capacity. On the basis of these conflicting results, it is possible that the XPD variants are not predictive of a specific phenotype but rather are prognostic and associated with other DNA sequence variants that are implicated in the repair of platinum complexes.

TAMOXIFEN AND SULTOTRANSFERASE
Tamoxifen is currently used in the treatment of all stages of hormone-dependent breast cancer as well as in the prevention of breast cancer. It acts as a result of metabolism to form its primary metabolite, 4-hydroxytamoxifen (4-OH-tam), which is approximately 100-fold more potent as an antiestrogen than is tamoxifen.

Among the 4 major sulfotransferases (SULTs) expressed in the human liver, SULT1A1 is known to play the most important role in the hepatic cytosolic trans-selective sulfation of 4-OH-tam isomers. Recent data suggest that the SULT1A1 gene is highly up-regulated by 4-OH-tam in ZR75-1 breast cancer cells. A single nucleotide polymorphism in the SULT1A1 open reading frame results in an Arg to His substitution at codon 213. Individuals homozygous for the His allele have approximately a 10-fold lower phenol SULT activity compared with that of individuals with the high-activity allele (SULT1A1*2). Among women receiving tamoxifen for adjuvant treatment of breast cancer, those homozygous for the SULT1A1*2 low-activity allele had approximately 3 times the risk of death (hazard rate, 2.9; 95% confidence interval, 1.1-7.6) as did those homozygous for the common allele or those who were heterozygous (SULT1A1*1/*2). Among patients who did not receive tamoxifen, there was no association between survival and SULT1A1 genotype (hazard rate, 0.7; 95% confidence interval, 0.3-1.5).

The result of this study is somewhat counterintuitive. Because the SULT1A1 isoform is involved in the hepatic cytosolic trans-selective sulfation of 4-OH-tam isomers, one might expect higher circulating levels of 4-OH-tam for patients homozygous for the low-activity allele and therefore a greater antitumor effect. However, because the study examined the impact of the SULT1A1*2 polymorphism on the adjuvant treatment of breast cancer, it was not possible to evaluate tumor response rates. Therefore, patients with the low-activity allele receiving tamoxifen for metastatic disease might still be expected to have higher response rates but greater long-term risk for toxicity. One possible explanation relates to the global induction of the SULT1A1 enzyme by tamoxifen, the result of which may facilitate the detoxification of substances known to be substrates for the SULT enzyme, including estrogenic substrates. Further prospective studies evaluating the impact of the SULT1A1 pharmacogenetics on clinical outcomes are needed to confirm and clarify these observations.
CONCLUSIONS
The convergence of pharmacogenetics with rapid advances in human genomics has resulted in the ongoing transformation of pharmacogenetics into pharmacogenomics. With completion of the Human Genome Project and with the ongoing annotation of those data, the time is rapidly approaching when the sequences of virtually all genes encoding enzymes that catalyze phase 1 and 2 drug metabolism will be known. The same will be true for genes that encode drug transporters, drug receptors, and other drug targets. As a result, the traditional phenotype to genotype pharmacogenetic research paradigm described at the beginning of this article is reversing direction to create a complementary genotype to phenotype flow of information. For example, a recent pharmacogenetic research strategy involves sequencing genes that encode proteins that might influence drug effect using DNA samples from large numbers of subjects of differing ethnicities to identify common sequence variation within those genes. That step is followed by functional genomic studies designed to determine which of those common gene sequence variants might be of functional importance. The next and perhaps most difficult step is the translation of this genomic and functional genomic information into well-controlled clinical studies designed to determine which of the common sequence variants that appear to be of functional importance have clinical meaning when present in patients exposed to drugs. Although most of the current applications of pharmacogenetics focus on single enzyme deficiencies and their role in predicting toxicity, most drug effects are determined by the interplay of several gene products that govern the pharmacokinetics and pharmacodynamics of medications. Therefore, current and future studies need to examine the effect of the variation of multiple different genes involved in the uptake, distribution, metabolism, and actions of these drugs. Finally, although the promise of pharmacogenetics and pharmacogenomics has yet to be fully achieved, there is little doubt that medicine stands on the verge of a time when health care professionals will routinely have ready access to gene sequence information that, when applied properly, has the potential to improve their ability to select the optimal drug at the optimal dose for each patient. As a result, pharmacogenetics and pharmacogenomics promise fundamentally to alter rational drug therapy.

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