Allelic Expression of Phase II Metabolizing Enzymes and Relationship to Irinotecan Toxicity

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Many drugs are associated with variable response rates and, of the 1,200 drugs approved for use in the United States, about 15% are associated with adverse drug responses (Jorde, Carey, & Bamshad, 2010c). Often, variable response and risk for toxicity can be explained because of differences in genes and in the proteins encoded by those genes. Single nucleotide polymorphisms (SNPs) responsible for variable expression can be found in genes encoding for drug targets (receptors) or in genes responsible for drug disposition, including those that encode metabolizing enzymes or transporter molecules (Jorde et al., 2010c; Kuo, Lee, & Ma, 2009; Ma & Lu, 2011). Although pharmacogenetics usually refers to drug interactions based on a relatively small number of genes, pharmacogenomics is the preferred term because it refers to interactions within the entire complement of genes (Krau, 2013; Ma & Lu, 2011). This article discusses how SNPs in phase II metabolizing enzymes can influence irinotecan-induced toxicity.

Metabolism of Drugs

Phase I metabolism is an oxidation-reduction process that, in most cases, converts the active drug into inactive metabolites, discontinuing the action of the drug. This process is, primarily, a function of enzymes from the cytochrome p450 (CYP) system. SNPs encoding CYP2D6, CYP2C9, and CYP2C19 are well-studied and have implications for a number of common drugs.

Enzymes responsible for phase II metabolism are conjugating enzymes. They form covalent linkages between the phase I metabolite and endogenous chemical molecules, like hydrogen, sulfate, glucose, or acetate (Correia, 2012). Phase II compounds are generally inactive, and they are highly polar, enabling the metabolite to be eliminated through the urine or feces. Insufficient production of these enzymes means phase I metabolites circulate longer, putting the drug recipient at greater risk for toxicity.

Genetic Polymorphisms

Every protein made by the body has a "recipe" (gene) at a specific chromosome location, known as the locus. Adenine (A), guanine (G), cytosine (C), and thymine (T) are the nucleotide building-blocks of the DNA double helix, and they are the basic components of each "recipe" in the body. Nucleotide chains can be rearranged (e.g., ACCAAGTGC, CACCTGGAT) in enough configurations to make the 20,000–25,000 genes found in the human body (Jorde, Carey, & Bamshad, 2010a). Changes in any of these can change the configuration or function of the final gene product, the protein. For example, a single-nucleotide substitution can change GUU (guanine, uridine, uridine), the RNA recipe for valine, to GAU (guanine, adenine, uridine), the RNA recipe for glutamate. This SNP is responsible for the hemoglobin changes associated with sickle cell disease (Jorde, Carey, & Bamshad, 2010b) and is but one of thousands possible in the human genome. Polymorphisms can affect single or multiple nucleotides within the genetic recipe. Mutations in genes encoding phase II metabolizing enzymes can affect an individual’s ability to effectively excrete phase I metabolites.

Uridine Diphosphate Glucuronosyltransferases

Human uridine diphosphate glucuronosyltransferases (UGT) is a superfamily of conjugating metabolizing (phase II) enzymes. UGT catalyzes the transfer of glucuronic acid to the functional group (hydroxyl, carboxyl, amino, or sulfur) of a drug substrate. This facilitates excretion of the metabolite into the urine or bile by increasing its polarity (Court, 2007; Li & Bluth, 2011; Ma & Lu, 2011). To date, 17 human UGT genes have been identified, and they are classified into two subcategories, UGT1 and UGT2 (Li & Bluth, 2011). Polymorphisms, or genetic variants, have been identified for almost all members of the UGT family, and each can affect the function or expression of the protein.

UGT1A1 is a gene that encodes UGT and is responsible for the conjugation of bilirubin and many drug compounds (Court, 2007; Li & Bluth, 2011; Ma & Lu, 2011). Decreased catalytic activity of UGT puts individuals expressing low-functioning UGT1A1 variants (alleles) at greater risk for drug toxicity. UGT1A1*28 and UGT1A1*6 are two such variants with significance to oncology. Each of these alleles is associated with decreased glucuronidation (inactivation) of SN-38, the active metabolite of irinotecan (Court, 2007; Li & Bluth, 2011; Ma & Lu, 2011). Decreased UGT1A1 activity means that SN-38 cannot be effectively converted to its β-glucuronide derivative, necessary for its excretion (Li & Bluth, 2011). The UGT1A1*28 polymorphism is found in the gene’s promoter region. The promoter region is found immediately upstream of the genetic recipe. RNA polymerase binds to this promoter region on DNA to begin the transcription process (copying RNA from DNA). The transcribed RNA will then be read by the ribosomes to make the protein, in this case UGT. Polymorphisms in the promoter region will not affect the recipe.
Asians (Li & Bluth, 2011; Ma & Lu, 2011). Gilbert's syndrome affects ap-
approximately 10% of Caucasians, and 13%–16% of Asians will have at least one UGT1A1*28 allele. People with Gilbert's syndrome, a syndrome characterized by a polymorphism associated with mild infantile hyperbilirubinemia, have two copies of the UGT1A1*28 allele, and, therefore, have significantly reduced UGT production, with much greater risk of drug toxicity (Court, 2007; Li & Bluth, 2011; Ma & Lu, 2011). Gilbert's syndrome affects approximately 10% of Caucasians.

UGT1A1*6 is another variant of the UGT1A1 gene. In the UGT1A1*6 allele, a glycine (WT) in the gene's amino acid sequence is replaced by arginine, changing the function of the final protein (Li & Bluth, 2011; Ma & Lu, 2011). This SNP is associated with decreased UGT1A1 catalytic activity, putting UGT1A1*6 heterozygotes and homozygotes at increased risk over WT homozygotes for drug toxicity. UGT1A1*6 is found in less than 1% of Caucasians and about 16%–23% of Eastern Asians (Li & Bluth, 2011; Ma & Lu, 2011).

Irinotecan

Irinotecan is a topoisomerase I inhibitor widely used in the treatment of metastatic colorectal cancer as well as in advanced non-small cell lung cancer (Li & Bluth, 2011). Irinotecan therapy is associated with a number of toxicities, the most significant being diarrhea and myelosuppression. UGT1A1*28 and UGT1A1*6 homozygotes have been identified as having a significantly greater risk of diarrhea and myelosuppression, compared to WT homozygotes (Court, 2007; Li & Bluth, 2011; Ma & Lu, 2011).

Comparing the two identified alleles, UGT1A1*28 is of greater concern. In 2005, the U.S. Food and Drug Administration (FDA) added pharmacogenomic labeling, in relation to UGT1A1*28 expression, to the prescribing information for irinotecan (Pfizer, 2012). A warning label has been added to the drug's package insert recommending an initial dosage-reduction for known UGT1A1*28 homozygotes (Pfizer, 2012). The prescribing information does not address UGT1A1*6 considerations. The FDA does not mandate testing for UGT1A1*28 or UGT1A1*6 at this time. The National Comprehensive Cancer Network (2014) recognizes that use of testing in clinical practice has not been established and does not recommend testing in those who have exhibited irinotecan toxicity because a dose reduction will already be required.

Nursing Implications

Nurses who administer irinotecan are certainly aware of variable drug response related to this therapy. Although a strong association exists for the risk of myelosuppression with the expression of UGT1A1*28, little clinical evidence demonstrates how these studies should guide irinotecan dosages. Clinical trials are needed to determine how irinotecan doses should be adjusted when UGT1A1 activity is known. Clinical studies are likely to show that UGT1A1*28 homozygotes require lower doses than heterozygotes; although, some evidence shows that the risk diminishes with repeated administration (Court, 2007). Until clinical trials can help define dosing algorithms based on allelic expression, pharmacogenomic testing prior to irinotecan therapy is not recommended. However, as this science develops, nurses should be mindful that they are likely to see increased incidence of pharmacogenomic testing to determine drug dosages and to predict risk of toxicities.

When administering irinotecan to those with Gilbert's syndrome, the nurse should monitor the client closely for evidence of myelosuppression. The nurse should be vigilant in teaching these patients about means to prevent infection and should inform patients to immediately report any chills or fevers. UGT1A1*28 homozygotes are also at greater risk for diarrhea, so patient education should include information about hydration and diarrhea management. Patient education and vigilant monitoring will remain the standards of care while pharmacogenomic studies are validated in clinical-use studies.

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References


