Application of Pharmacogenetics to Optimization of Mercaptopurine Dosing

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The traditional approach to dosing anticancer drugs is to administer a standard starting dose, which is normalized to body surface area, and then to adjust or individualize subsequent doses to account for the severity of ensuing drug toxicity. Dosing according to body surface area is based on the assumption that the volume of distribution and drug elimination mechanisms are proportional to the body surface area. However, pharmacokinetic studies of anticancer drugs typically reveal substantial interpatient variability in plasma drug concentrations when the dose is based on body surface area (1). The potential consequences of this variability in systemic drug exposure are life-threatening toxic effects in patients who are exposed to overly toxic drug concentrations and tumor progression in patients who achieve subtherapeutic drug concentrations. The identification of specific factors that account for variability in drug disposition among patients can lead to more rational dosing methods such as adaptively dosing carboplatin based on glomerular filtration rate.

For the purine analogue mercaptopurine, which is used to maintain remission in childhood acute lymphoblastic leukemia (ALL), the standard starting dose is 75 mg/m² day orally, and subsequent dose adjustments are based primarily on the degree of suppression of the neutrophil count. Plasma mercaptopurine concentrations after oral administration of the drug are highly variable (2–4). The area under the plasma concentration–time curve (AUC), which is a measure of systemic drug exposure, can vary by as much as 70-fold in a homogeneous population of children, who are dosed in a uniform manner (4). Mercaptopurine pharmacokinetic variability has prompted studies (4–6) to investigate the relationship between pharmacokinetic parameters, such as AUC, and disease outcome. These studies have failed to define a role for therapeutic drug monitoring or to identify more rational a priori adaptive dosing methods based on patient characteristics for mercaptopurine, in part because of the substantial intrapatient variability in mercaptopurine pharmacokinetics (4).

Mercaptopurine is a prodrug that must be converted intracellularly to its thioguanine nucleotide form to exert a cytotoxic effect (7). The competing pathways for mercaptopurine activation and catabolism are shown in Fig. 1. Oxidation to thiouric acid by xanthine oxidase is the primary catabolic pathway. Extensive presystemic (first-pass) metabolism of mercaptopurine by xanthine oxidase also limits the bioavailability of oral mercaptopurine (2). The first step in the intracellular activation of mercaptopurine is catalyzed by hypoxanthine–guanine phosphoribosyltransferase, which yields thioinosine monophosphate (TIMP). TIMP is subsequently converted to thioguanine triphosphate, which is incorporated into DNA. Although methylation of the thiol group on mercaptopurine and TIMP by thiopurine methyltransferase (TPMT) yields metabolites that can inhibit steps in the purine salvage pathway, thiol methylation is the initial step in primarily catabolic pathways for mercaptopurine and TIMP. Methylation competes with the activation pathway and modulates the size of the active thioguanine nucleotide intracellular pools in the target cells.

Erythrocyte levels of mercaptopurine-derived thioguanine nucleotides have been monitored in children receiving oral mercaptopurine therapy. Erythrocyte thioguanine nucleotide levels exhibit substantial interpatient variability and are associated with the degree of myelosuppression and, in some studies, with the risk of relapse (8–10). However, variability in erythrocyte thioguanine nucleotide levels is not related to variation in the dose or AUC of mercaptopurine, to patient age, or to sex (4). The lack of relationship between mercaptopurine dose and erythrocyte thioguanine nucleotide level indicates that modifications of mercaptopurine dose may not have a predictable or proportional effect on erythrocyte thioguanine nucleotide levels; therefore, measurement of erythrocyte thioguanine nucleotide levels has not been useful for individualizing the dose of mercaptopurine.

Methylation of drugs is a common metabolic pathway, as evidenced by the fact that more than 100 methyltransferase enzymes have been identified (11). TPMT, which catalyzes the S-methylation of aromatic and heterocyclic compounds, utilizes S-adenosylmethionine as a methyl donor. Measurement of TPMT activity in erythrocytes led to the discovery that TPMT is genetically polymorphic. This was subsequently confirmed through genotyping (12,13). At least eight variant alleles of TPMT with low enzyme activity have been cloned and sequenced (11), and the gene frequency of the variant alleles is 6%. The functional significance of this TPMT polymorphism was observed in the one in 300 patients who are homozygous for the low enzyme activity variant alleles. These patients have markedly elevated erythrocyte thioguanine nucleotide levels and experience severe and often life-threatening toxic effects when treated with standard doses of thiopurines (14), but they will tolerate these agents at drastically reduced dose levels. On the basis of this observation and studies that demonstrated that TPMT activity in erythrocytes is predictive of enzyme activity in other tissues, erythrocyte TPMT activity is measured before the initiation of thiopurine therapy at many centers to identify the 0.3% of patients who are at high risk for excessive thiopurine-induced toxicity (11).

In this issue of the Journal, Relling et al. (15) provide evi-
Categorizing patients according to genotype for relatively uncommon polymorphisms will only identify a small subset of patients who would benefit from pharmacogenetically guided dosing, whereas phenotyping patients by estimating enzyme activity may also allow for individualization of drug doses within the population of patients with homozygous wild-type genotype. For some drug-metabolizing enzymes, there is a wide range of enzyme activity within the wild-type group, as is the case with TPMT, and many drug-metabolizing enzyme systems are inducible. Assessing the relationship between TPMT activity and mercaptopurine dose in a manner similar to the analysis shown in Fig. 4 by Relling et al. (15) for thioguanine nucleotide levels may identify a subpopulation within the TPMT wild-type group who could also benefit from adaptive dosing based on erythrocyte TPMT levels.

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