The vinca alkaloid vincristine has been an essential component of the treatment of pediatric acute lymphoblastic leukemia (ALL) since combination chemotherapy first came into widespread use in the 1960s. Because vincristine has robust activity against both solid tumors and other malignant conditions, and because its lack of myelosuppression makes it suitable for combining at full doses with other myelosuppressive drugs, vincristine remains one of the most widely used anticancer agents. However, the neurotoxic effects of vincristine (and other microtubule-targeting agents), including both sensory and motor peripheral neuropathies, continue to have a major impact on our ability to deliver vincristine at fully effective doses and dose intensities. A pharmacogenomic explanation of susceptibility to vincristine neurotoxicity would offer the potential for individualized dosing, which in turn might improve outcomes. A number of genes implicated in various aspects of vincristine metabolism have been evaluated for an association with neurotoxic effects. One particular gene of interest is CYP3A5. Egbelakin et al performed CYP3A5
genotyping in 107 children with ALL; limited vincristine pharmacokinetics were analyzed in 74 patients. Expressers of active CYP3A5 enzyme experienced less vincristine-induced neurotoxicity than non-expressers, and CYP3A5 expressers had faster rates of vincristine conversion to metabolites and faster vincristine clearance, potentially resulting in lower vincristine exposure compared with CYP3A5 non-expressers. While there were insufficient numbers of African Americans in this study to examine effects of race on the outcomes, CYP3A5 is expressed more frequently in African Americans than whites, which could explain the observation in other studies that African American children have less vincristine-induced neurotoxicity than white children. Other studies investigating CYP3A5 polymorphisms and vincristine toxic effects, however, have been inconclusive.3,4

In a recent issue of JAMA, Diouf et al5 presented an important study that demonstrated an association between a genetic polymorphism and vincristine-related peripheral neuropathy in children with ALL. This study is notable for a number of reasons. First, it uses an agnostic genomewide association study approach rather than a candidate gene approach to the analysis of genetic contributions to vincristine neurotoxicity. Second, the investigators identify an inherited polymorphism in the promoter region of CEP72 that is associated with increased risk and severity of vincristine-related peripheral neurotoxic effects. The CEP72 gene encodes a centrosomal protein involved in microtubule formation; thus its relationship with the toxicity of a microtubule-targeting agent is inherently plausible. Notably, the frequency of the risk allele was lower in African American participants in this study. Third, the investigators returned to the bench to confirm that CEP72 expression affects cells’ sensitivity to vincristine. They demonstrated that when CEP72 expression is impaired using short hairpin RNA, neurons derived from human-induced pluripotent stem cells show significantly greater sensitivity to vincristine. In addition, decreased expression of CEP72 in 2 human ALL cell lines was associated with increased sensitivity to vincristine, and primary leukemia cells from patients homozygous for the CEP72 risk allele were also more sensitive to vincristine. Thus this study provides not only evidence of a statistical association between a genetic polymorphism and a drug toxicity phenotype, but also a plausible explanation for and supportive in vitro evidence of the relationship. In contrast, CYP3A5 was not significantly associated with vincristine neurotoxic effects in this study.

Perhaps we should not be surprised when differently designed studies demonstrate plausible, and apparently conflicting, explanations of genetic determinants of anticancer drug toxicity. Blanco et al6 showed that patients with carbonyl-reductase polymorphisms were at an increased risk of cardiomyopathy even after low cumulative anthracycline doses. In contrast, in a simultaneously published article, Visscher et al7 found 4 single-nucleotide polymorphisms that were associated with increased risk of anthracycline cardiotoxic effects and 5 with a protective effect, but carbonyl-reductase polymorphisms were not among these 9. As an editorial accompanying that pair of articles pointed out, the different definitions of cardiac toxic effects used in the 2 studies might explain the differences in results.

Similar issues with toxic effects end points may affect analyses of vincristine neurotoxicity. Chemotherapy-induced neurotoxic effects are difficult to measure objectively. Grading sensory neuropathy requires that the patient be able to report paresthesias, pain, or numbness, which may be particularly difficult for young children, who make up the majority of patients diagnosed with pediatric ALL. In addition, the investigator must determine whether these sensory events are adequately controlled with various interventions and whether they interfere with daily function. Finally, in many studies, information on neurotoxic effects is collected retrospectively from the medical record, which results in decreased data quality.

What are we to make of the apparently conflicting data on pharmacogenomic associations with vincristine-related neuropathy? It is worth considering whether all these associations could be correct, even if they are not detected in every study. Polymorphisms of CYP3A5 could exert their influence through altered pharmacokinetics, while the CEP72 polymorphism would have a pharmacodynamic effect in terms of determining patient sensitivity to vincristine toxicity. Vincristine is already known to have another important pharmacodynamic mediator of toxicity, namely Charcot-Marie-Tooth (CMT) syndrome, which can predispose patients to severe vincristine neurotoxic effects. Interestingly, at least 2 genes associated with CMT syndrome, dnm2 and KIF1B, are also associated with microtubules. It seems more likely than not that in many cases, genetically predicted variability in drug metabolism and genetically determined susceptibility to the effects of exposure to drug and metabolites will combine to produce the phenotype of sensitivity to drug toxicity. This does not mean that we should give up trying to find genotype-phenotype correlations but rather that we must embrace the challenge of elucidating all the potential mechanisms at work if we are to arrive at truly personalized medicine.