Primary genetic abnormalities of leukemic cells are well recognized to have important prognostic and therapeutic significance. Host factors can also influence treatment efficacy. For example, given the same dosages of mercaptopurine or methotrexate, reduced accumulation of active metabolites in leukemia cells, due to fast clearance, inactivation, or other reasons, has been associated with a poor outcome in acute lymphoblastic leukemia (ALL). The concomitant administration of certain anticonvulsants (e.g., phenytoin, phenobarbital, or carbamazepine) increases the systemic clearance of antileukemic agents by inducing the production of cytochrome P-450 enzymes, and therefore leads to poor treatment outcome of ALL. Conversely, azole antifungal agents inhibit these enzymes, thereby increasing the efficacy or toxicity of chemotherapy such as vincristine.

Germline polymorphisms in genes that encode for the proteins involved in the pharmacodynamics of antileukemic agents are common, with the frequency of the “variant” allele ranging from 5% to 50%. Alterations of the activity or function of drug-metabolizing enzymes, transporters, receptors, and drug targets result in wide differences among patients in terms of drug disposition and pharmacologic effects, and thereby influence the efficacy or toxicity (or both) of antileukemic agents. Traditionally, pharmacogenetic studies have focused on single gene candidates, based on the pharmacokinetic characteristics of a specific drug. Increasingly, a broader strategy, also termed pharmacogenomics, is used to identify the entire set of genes that are relevant to the pharmacological effects of a given drug.

In ALL, the best-studied example of pharmacogenetics is the relation between polymorphisms in thiopurine methyltransferase (TPMT) which catalyses the S-methylation (inactivation) of mercaptopurine and other thiopurines, and the clinical response. Patients who inherit homozygous deficiency of this enzyme require dose reduction of mercaptopurine by 90% to 95% to avoid severe hematopoietic toxicity. Patients with heterozygous deficiency also have a significantly increased risk for hematopoietic toxicity, but they tend to have a better treatment response than do those without this inherited deficiency, possibly because they receive a higher dose intensity of mercaptopurine. In fact, the TPMT genotype was linked to early response in a study as assessed by minimal residual disease level on day 78 of remission induction which included mercaptopurine treatment for only 4 weeks. Patients with wild-type alleles were 2.9 time more likely to have positive minimal residual disease than those with heterozygous genotype. Notably, TPMT deficiency has also been linked to a higher risk of second malignancies in patients with ALL, including therapy-related acute myeloid leukemia, and radiation-induced brain tumors.

Isoenzymes of the glutathione S-transferase (GST) superfamily inactivate many electrophilic endogenous substances and xenobiotics, including many antileukemic drugs such as anthracyclines, topoisomerase II inhibitors, cyclophosphamide, by conjugating them to glutathione. Although they generally detoxify reactive metabolites, they also play a role in forming cytotoxic metabolites. The null genotype of these enzymes has been associated with a favorable response to prednisolone, and to a reduced risk of relapse in children with ALL. A tandem-repeat polymorphism within the enhancer region of the thymidylate synthase gene, one of the major targets of methotrexate, has been linked to increased expression of the enzyme and an increased risk of relapse. However, the prognostic importance of these pharmacogenetic variables is treatment-
dependent, and might also be influenced by other genotypes in the context of combination chemotherapy.\textsuperscript{19,20}

A number of other pharmacogenetic factors have been associated with outcome. Homozygosity for a polymorphism of methylenetetrahydrofolate reductase was associated with an increased risk of oral, gastrointestinal, or hepatic adverse effects after low-dose methotrexate,\textsuperscript{21,22} and with greater in vitro sensitivity of leukemic blasts to methotrexate.\textsuperscript{23} The vitamin D receptor Fok I start site CC genotype and thymidylate synthase low activity 2/2 enhancer repeat genotype were associated with an increased risk of osteonecrosis.\textsuperscript{24}

Global gene expression profiling of leukemic cells and normal tissue can reveal new dimensions of the pathologic features of leukemic cells, identify new targets for anticancer drugs, and disclose previously unrecognized genomic determinants of cancer-drug resistance and host toxicity. Since drug responses are influenced by multiple genes, polygenic studies and models will be increasingly required to fully elucidate the genetic determinants of drug response.\textsuperscript{7} In this regard, the recently available oligonucleotide SNP array\textsuperscript{25} and the large scale public genetic databases such as the HapMap project will facilitate these investigations. Finally, it should be recognized that acquisition of additional chromosomes in leukemia cells can create discordance between germ-line genotypes and leukemia-cell phenotypes, including pharmacogenomics.\textsuperscript{26}

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