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Genetics of Childhood Acute Lymphoblastic Leukemia

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Abstract

Genetic alterations that underlie the pathogenesis of individual leukemia subtypes have important prognostic implications in acute lymphoblastic leukemia (ALL). Heretofore, specific genetic abnormalities with prognostic relevance were identified mainly by cytogenetic analysis or reverse-transcriptase polymerase-chain-reaction, and were largely limited to B-lineage ALL cases. Moreover, there is heterogeneity among specific genetic subtypes of ALL and treatment has over-riding impact on the prognostic information conveyed by the genetic abnormalities. In Philadelphia chromosome-positive (Ph^+) ALL, an age of 1 to 9 years and a low initial leukocyte count confer a favorable prognosis. In each category of 11q23/*MLL* abnormality, infants less than 1 year of age have a worse treatment outcome than do older patients. Allogeneic transplantation with HLA-matched related donor improved outcome for patients with Ph^+ ALL but not those with the t(4;11) and *MLL-AF4* fusion. Using oligonucleotide microarrays, T-cell ALL can now be classified into four major subtypes with prognostic significance: *MLL-ENL* and *HOX11* clusters with favorable prognosis and *TAL1* and *LYL1* clusters with inferior outcome. In our recent study of 327 ALL cases, distinct expression profiles could not only accurately identify each of the known prognostically important leukemia subtypes, but also individual cases that would eventually relapse or develop therapy-related acute myeloid leukemia. We have also identified a novel ALL subgroup with unique expression profile. Examination of the genes comprising the different expression signatures provided important insights into the biologic differences between the leukemia subgroups. The importance of host pharmacogenetics has also been recognized. Thus, genetic polymorphisms of certain drug-metabolizing enzymes, drug transporters or drug receptors have been linked with treatment efficacy and toxicity, as well as host susceptibility to the development of de novo leukemia or therapy-related second cancers. The best-characterized genes (e.g. thiopurine methyltransferase, cytochrome P450, glutathione transferase, methylenetetrahydrofolate reductase and NAD(P)H: quinone oxidoreductase) will be discussed. Ultimately, patients will be treated with individualized therapy based on leukemic cell gene expression profile and host pharmacogenetics.