Genotype predicts treatment related mortality (TRM) in African-American and Asian pediatric AML patients

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New research suggests that the presence of a specific genetic marker, known as WT1 SNP rs16754, may be associated with reduced toxicity from chemotherapy in African-American and Asian children with acute myeloid leukemia (AML).

AML, the second most common form of leukemia in children, is a blood cancer in which the bone marrow makes a large number of abnormal white blood cells that crowd out other healthy blood cells over time, leading to infection, anemia, or excessive bleeding. Although 60 to 70 percent of children with AML achieve long-term remission after treatment with multi-agent chemotherapy, the treatment-related mortality (TRM) associated with this intensive treatment regimen remains a major concern for this patient population. Recently, researchers have developed models that use sophisticated genome sequencing techniques to better understand how patients' genetic makeup may influence their risk of TRM.

The WT1 gene, a tumor suppressor that regulates cell growth, can be subject to "loss-of-function" mutations that lead to the development of AML. Unlike genetic mutations, single-nucleotide polymorphisms (SNPs, naturally occurring variations in the DNA that determine an individual's unique genetic makeup) are not typically thought to play a role in leukemia development or treatment response. However, researchers recently discovered that the presence of SNP rs16754 in the

WT1 gene is correlated with improved outcomes in pediatric patients with AML. Based on the fact that the frequency of SNP rs16754 varies by race, researchers assessed the effect of this SNP on outcomes in specific ethnic patient groups.

To determine if the presence of SNP rs16754 affected survival, remission, relapse risk, and TRM in pediatric AML patients of different ethnicities, a team of investigators analyzed the DNA of 492 children with AML enrolled in the CCG-2961 protocol, a Phase III Children's Cancer Group trial. The intensive treatment regimen delivered to patients during CCG-2961 allowed researchers to study the effects of ethnicity on patient outcome, while minimizing non-biological influences such as access to care or oral medication compliance. Of the 492 patients, 138 (28%) had the SNP rs16754 (SNP+). After stratifying the patients by ethnicity, the investigators found that the presence of SNP rs16754 varied by race, with 53 percent of Asians, 34 percent of Hispanics, 25 percent of Caucasians, and 21 percent of African Americans carrying the genetic variation. The SNP+ patients had higher five-year overall survival rates than those without the variation (SNP-) (61% vs. 44%). Within each racial subgroup, the five-year overall survival rate was higher in the SNP+ patients.

Although survival improvements in leukemia clinical trials are often attributed to increased remission rates or decreased relapse, remission and relapse rates did not differ significantly between SNP+ and SNP- patients in this study. The investigators examined whether the SNP had any association with TRM and found that TRM rates did not differ by SNP rs16754 genotype when all ethnicities were considered together. However, TRM rates in SNP+ African-American and Asian patients, when taken together, were significantly lower than in SNP- patients of those two ethnicities. African-American and Asian patients without SNP rs16754 had significantly higher rates of treatment-related toxic death compared to SNP+ patients (African-American: 25% vs. 0%; Asian:

43% vs. 0%). These results suggest that the protective effect of the presence of SNP rs16754 in reducing chemotherapy-related toxicity in pediatric AML patients is more pronounced in those of African-American and Asian descent.

"Identifying the patient-specific factors that can affect responses to treatment in different patients with the same disease brings us closer to our goal of designing personalized treatments that provide the most therapeutic benefit with the least amount of toxicity to these children," said Phoenix Ho, MD, lead author and Attending Physician at Seattle Children's Hospital in the Division of Pediatric Hematology/Oncology at the University of Washington School of Medicine and Research Associate at the Fred Hutchinson Cancer Research Center in Seattle. "Our analysis was conducted on a trial completed in 2002, and treatment protocols for pediatric AML have evolved since that time. Our next step is to validate our findings by studying this same association in contemporary trials. We are also designing studies to uncover the mechanism behind the association between the SNP and reduced toxicity, with the hope of translating these findings into improved treatments for pediatric AML."

Provided by American Society of Hematology

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