Age impacts pharmacogenomics and treatment outcomes for most common form of leukemia

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Jun J. Yang, PhD, St. Jude Departments of Pharmacy and Pharmaceutical Sciences and Oncology and first co-authors Zhenhua Li, PhD, and Satoshi Yoshimura, MD, PhD, demonstrated that treatment and age impact outcomes for B-cell acute lymphoblastic leukemia. Credit: St. Jude Children's Research Hospital
Acute lymphoblastic leukemia (ALL) affects both children and adults, but children have better chances to be cured, with long-term survival rates of over 85% compared to 50%–75% in adults.

Scientists at St. Jude Children's Research Hospital conducted a comprehensive study to understand the biological causes driving this difference. The work, published today in the *Journal of Clinical Oncology*, provides a blueprint for understanding B-cell acute lymphoblastic leukemia (B-ALL), the most common form of the disease.

"Our study provides a pharmacological and biological explanation of why the survival rate of ALL becomes progressively worse as age increases," said corresponding author Jun J. Yang, Ph.D., St. Jude Departments of Pharmacy and Pharmaceutical Sciences and Oncology.

ALL affects the blood and bone marrow by overproducing immature lymphocytes, a type of white blood cell. Scientists have long observed age-related differences in B-ALL outcomes, but the reasons why remained unclear.

"ALL is one of few cancers that can occur throughout development, but in adults it is significantly more lethal," Yang said. "Many of us have assumed that adult ALL may be differentially resistant to standard treatments, but it had never been tested comprehensively until our study."

**Drug sensitivity across age groups**

The researchers examined 767 children and 309 adults diagnosed with B-ALL, assessing the leukemia cells' sensitivity to 21 drugs. Through this work they identified 23 ALL molecular subtypes using RNA sequencing.
"First, seven of the 21 drugs showed drastic differences in their ability to kill leukemia cells between children and adults," explained co-first author Satoshi Yoshimura, MD, Ph.D., St. Jude Department of Pharmacy and Pharmaceutical Sciences. "For example, pediatric ALL samples are generally more sensitive to asparaginase, mercaptopurine, and prednisolone, compared to samples from adult patients."

The researchers discovered that differences in the potency of certain drugs correlate with the molecular subtypes of B-ALL.

"We found that, for the majority of the cytotoxic drugs with differential activity between adult and pediatric, it's largely explained by the age-related differences in the underlying genomic abnormalities of their cancer," Yang said.

**Pharmacogenomics and age in B-ALL**

But the story did not end here, because the molecular subtype of ALL did not explain 100% of the differences in leukemia drug sensitivity between children and adults. For example, DUX4 gene rearrangement can happen in both childhood and adult ALL, but cases in adults are more drug-resistant because a set of genes are uniquely turned on when patients get older.

Imagine the treatment for B-ALL as tending to a vegetable garden. Among the seeds (healthy cells) are weeds (molecular subtypes of B-ALL). Although the plants might be the same, other factors, such as soil quality (age), can vary between two gardens. A pesticide that kills weeds in one garden might not work in another because of the different soil conditions.

The researchers found that some children had "adult-like" ALL based on their gene expression profiles, making them more resistant to treatment
and leading to poorer outcomes. This suggests that both age and individual genomics must be considered to predict treatment response.

"There's a lot of heterogeneity within each age group," explains Yang. "You cannot simply divide patients into older or younger than 18 and offer therapy on the basis of legal age of majority, you have to look at their underlying molecular characteristics and pharmacogenomic features."

**Tailoring treatment for patients with B-ALL**

Together the group's findings suggest the need for tailored treatment strategies for both children and adults with B-ALL. "This is the first time that such a large amount of pharmacogenomic data has been generated in a single effort looking at both children and adults," stated co-first author Zhenhua Li, Ph.D., St. Jude Department of Pharmacy and Pharmaceutical Sciences. "This gives us an opportunity to fairly compare them."

The study also highlights the importance of personalized medicine, "We successfully showed that adults are more resistant to conventional or cytotoxic drugs. We now urgently need to find new drugs that will work in adult ALL, given their resistance to standard therapy," noted Yoshimura.


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