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Drugs approved to treat other cancer types may improve treatment outcome for a type of childhood leukemia

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Tyrosine kinase inhibitors (TKIs) may improve treatment outcome for children and young adults with Ph-like acute lymphoblastic leukemia (Ph-like ALL), a disease with dismal prognosis, according to data presented at the American Association for Cancer Research special conference Hematologic Malignancies: Translating Discoveries to Novel Therapies, held Sept. 20-23.

"We recently described a subtype of B-cell acute lymphoblastic leukemia with very poor outcome that is characterized by genetic alterations involving tyrosine kinases, termed Ph-like ALL," said Kathryn Roberts, PhD, postdoctoral research associate in the Department of Pathology at St. Jude Children's Research Hospital in Memphis, Tennessee. "We wanted to examine whether these alterations contribute to the development of Ph-like ALL, and determine if they could be targeted with tyrosine kinase inhibitors.

"We showed for the first time that the kinase alterations we tested contribute to the development of Ph-like ALL, and that Ph-like ALL can be treated effectively with tyrosine kinase inhibitors in animal models," added Roberts. "These findings provide a strong rationale for treating Ph-like ALL patients with targeted therapies to improve their survival."

Roberts and colleagues conducted experiments in the laboratory using normal mouse blood cells and found that introduction of genetic

alterations to tyrosine kinases, enzymes that play an important role in cellular functions, caused the development of Ph-like ALL. With further experiments, they found that the different types of kinase alterations triggered different cell signaling pathways.

Next, they grew human Ph-like ALL tumors in mice, treated them with the TKI dasatinib, and found that the tumor burden reduced with treatment. As proof of principle, the STAT signaling pathway associated with the specific kinase alteration in the tumors was suppressed. The animal models used in these studies were newly developed by Roberts and colleagues.

"Our studies show that different FDA-approved TKIs such as imatinib, dasatinib, ruxolitinib, or crizotinib could potentially be used to treat Ph-like ALL patients, depending on the type of kinase alterations their tumors bear," said Roberts.

"We were able to gain a better understanding of the genetics underlying Ph-like ALL, and our studies could help identify patients who will not respond optimally to current therapy," added Roberts. "By knowing the exact genetic alteration upfront, we may be able to implement different therapeutic strategies to improve the survival rate of future patients with ALL."

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