Anti-malaria drug increases sensitivity of high-risk leukemic cells to targeted therapy

December 4 2017

First author Amit Budhraja, Ph.D., and senior author Joseph Opferman, Ph.D., determined that the anti-malaria drug (DHA) worked by repressing production of a protein (MCL-1) that promotes survival of a wide variety of cells, including cancer cells. Credit: St. Jude Children's Research Hospital

St. Jude Children's Research Hospital scientists have evidence that an anti-malaria drug sensitizes a high-risk subtype of acute lymphoblastic leukemia (ALL) to treatment with a promising class of targeted drugs,

raising hopes for more effective therapy. The findings appeared online this week in the journal *Clinical Cancer Research*.

The study focused on the ALL subtype BCR-ABL—positive ALL, also known as Philadelphia chromosome—positive ALL. BCR-ABL+ ALL has proven resistant to targeted therapies that have revolutionized treatment of other leukemias.

In this study, researchers showed not only that the widely used anti-malaria drug dihydroartemisinin, or DHA, sensitized BCR-ABL-positive ALL to the investigational drug ABT-263, marketed as Navitoclax, but how that happened.

Investigators reported the combination therapy had a synergistic effect on mouse and human BCR-ABL+ leukemic cell death and extended the lives of mice with the subtype. Compared to ABT-263 treatment alone, there was also no evidence of ABT-263 drug resistance in mice treated with the combination therapy.

"Survival rates for children and adults with this leukemia still lag, highlighting the urgent need for new therapies," said Joseph Opferman, Ph.D., an associate member of the St. Jude Department of Cell and Molecular Biology, who led the research. "Our findings suggest that combining DHA with ABT-263 can significantly improve treatment response."

The scientists determined that DHA worked by repressing production of a protein that promotes survival of a wide variety of normal and cancer cells. The protein, MCL-1, is elevated in many cancers and helps malignant cells resist a new class of drugs called BH3-mimetics that work by triggering programmed cell death via apoptosis.

"MCL-1 is widely recognized as an important survival molecule in many

normal cell types as well as cancer," Opferman said. "MCL-1 inhibitors are in development, but none are currently available for treating patients. And because MCL-1 is essential for proper functioning of many normal cell types, there is concern about potential toxicity. We sought to identify drugs that are available now to augment treatment of BCR-ABL-positive ALL."

BCR-ABL+ ALL accounts for about 5 percent of pediatric ALL and about 40 percent of ALL in adults. While overall survival for St. Jude patients with ALL is 94 percent, five-year survival is about 70 percent for children with BCR-ABL+ ALL and about 50 percent for adults. The path to a cure involves intensive chemotherapy and blood stem cell transplants.

ABT-263 belongs to a family of targeted therapies called BH3-mimetics. These drugs are designed to inhibit BCL-2; BCL-XL; and related proteins that, like MCL-1, promote cancer cell survival by blocking programmed cell death via apoptosis. But ABT-263 and other BH3-mimetics do not inhibit MCL-1.

The search for a drug to sensitize BCR-ABL+ ALL to ABT-263 and related compounds led Opferman and his colleagues to DHA. The drug is widely used to treat malaria, and a St. Jude drug screen showed DHA killed BCR-ABL+ ALL cells from mice.

Working in the laboratory, investigators in this study showed how DHA induced expression of a protein called CHOP that is a key regulator of the endoplasmic reticulum stress pathway in cells. CHOP expression triggered the stress pathway in BCR-ABL+ ALL cells from mice and led to suppression of MCL-1. "MCL-1 has a short half-life, so the cell's MCL-1 stores are rapidly depleted if the protein's translation is repressed," said first author Amit Budhraja, Ph.D., a postdoctoral fellow in Opferman's laboratory.

Now researchers are studying the mechanism in human BCR-ABL+ leukemic cells as well as in other cancers. "Identifying the mechanism will allow us to study the pathway in detail for other points to target for anti-cancer drug development," Opferman said.

More information: Amit Budhraja et al. Modulation of Navitoclax Sensitivity by Dihydroartemisinin-Mediated MCL-1 Repression in BCR-ABL+B-Lineage Acute Lymphoblastic Leukemia, *Clinical Cancer Research* (2017). DOI: 10.1158/1078-0432.CCR-17-1231

Provided by St. Jude Children's Research Hospital