Study finds pill may represent promising treatment for stubborn blood cancers

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A pill that suppresses a key regulator of cancer growth may provide hope to relapsed leukemia and lymphoma patients running out of treatment options for their aggressive, treatment-resistant disease, according to three reports* published online today in *Blood*, the journal of the American Society of Hematology.

Patients with blood cancer are typically administered a combination of chemotherapy and immunotherapy, the latter using the body's own immune system to help fight disease, as a first line of treatment. While chemotherapy has traditionally been successful in destroying cancer cells , it is accompanied by many harmful side effects and patients typically develop resistance, prompting researchers to investigate new targeted therapies that may be able to block the production of cancer cells while leaving normal cells unharmed.

One such targeted therapy, called idelalisib, is a highly selective compound that, unlike chemotherapy, can target a specific mechanism that fuels cancer growth. Taken as a pill, idelalisib first targets and then blocks the expression of the delta isoform of the PI3 kinase enzyme, which is critical for the activation and survival of cancerous B cells. Idelalisib's narrow targeting of the PI3 kinase delta make it an attractive potential therapy for patients with cancers that form in the B-cell pathway such as chronic lymphocytic leukemia (CLL), indolent non-Hodgkin lymphoma (iNHL), and mantle cell lymphoma (MCL). While idelalisib is currently under review by the U.S. Food and Drug Administration (FDA) for the treatment of treatment-resistant iNHL,

another drug in its class called ibrutinib, which specifically targets a different cell regulator, has been approved as a second-line therapy for CLL and MCL.

"Idelalisib is a part of a revolutionary new class of treatments that can hone in on a specific target without causing the wide range of side effects seen with chemotherapy," said study author Jennifer R. Brown, MD, PhD, Director of the Chronic Lymphocytic Leukemia Center at Dana-Farber Cancer Institute in Boston.

In three manuscripts published today in *Blood*, investigators present data from a large Phase I study evaluating the safety and efficacy of idelalisib in more than 150 patients with CLL, iNHL, and MCL. Before joining the trial, patients had received several previous treatments – some as many as 14 – that either failed to destroy the disease or provided only a temporary reprieve. After an initial study involving all trial participants, patients were separated into CLL, iNHL, and MCL disease cohorts and received varied doses of idelalisib. The therapy appeared to be effective, as patients suffered few side effects and demonstrated promising response rates, with 72 percent of CLL patients, 47 percent of iNHL patients, and 40 percent of MCL patients achieving either a complete or partial response.

"Considering the high number of previous therapies that these patients had received, higher than we sometimes see in comparable studies, the efficacy of idelalisib that we observed was remarkable," said study author Ian Flinn, MD, PhD, Director of the Hematologic Malignancies Research Program at Sarah Cannon Research Institute in Nashville and a widely recognized expert in lymphoma. "It was this initial excitement that has inspired further studies of this therapy in patients with treatment-resistant blood cancers."

While patients in the CLL and iNHL cohorts experienced significant and

prolonged reduction of disease activity, patients with MCL, a more aggressive and treatment-resistant type of lymphoma, experienced less favorable responses. Despite MCL patients' high overall response rate of 40 percent to idelalisib, the duration of their response to the drug was not as impressive; only a small fraction (22%) enjoyed prolonged benefits. Despite the modest duration of survival facilitated by idelalisib in the MCL group, the strong response rate suggests that investigators have identified a key regulator of cancer growth; however, more research is needed to further understand the potential of this therapy in MCL patients.

"While idelalisib is unlikely to receive designation as a single-agent therapy in mantle cell lymphoma due to the short duration of response, the path forward will likely include administering it in combination with other agents or developing second-generation PI3 kinase inhibitors," said study author Brad S. Kahl, MD, Director of the Lymphoma Service at the University of Wisconsin Carbone Cancer Center in Madison. "This study offers a strong foundation for future research on idelalisib in this disease."

More information:

- Idelalisib, an Inhibitor of Phosphatidylinositol 3-Kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia, Brown et al.
- Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-δ, as therapy for previously treated indolent non-Hodgkin lymphoma, Flinn et al.
- Results of a phase I study of idelalisib, a PI3Kδ inhibitor, in patients with relapsed or refractory mantle cell lymphoma (MCL), Kahl et al.

Provided by American Society of Hematology