MedicalXpress

Study confirms target of potent chronic leukemia drug

December 19 2013

A new study led by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) helps confirm that a molecule targeted by the experimental drug ibrutinib is critical for the development of chronic lymphocytic leukemia, the most common form of adult leukemia.

In clinical trials, ibrutinib has often shown exceptional activity in people with chronic lymphocytic leukemia (CLL). The agent targets a molecule called Bruton's tyrosine kinase (BTK). It permanently incapacitates the molecule, and this stops the transmission of an important signal that promotes cell growth and proliferation.

But ibrutinib also inhibits other molecules in CLL cells. Like BTK, these molecules are proteins called kinases, and they might be important for CLL-cell survival, the researchers say.

"Ibrutinib's lack of selectivity might mean that BTK is not the critical target in CLL, and that future drugs developed for CLL should focus on other molecules," says principal investigator Amy Johnson, PhD, associate professor of medicine in the division of hematology, and an OSUCCC – James researcher. However, the findings, published in the journal *Blood*, validated BTK inhibition.

"This study shows that BTK is an important therapeutic target in CLL," says first author Jennifer Woyach, MD, assistant professor in the

division of hematology and an OSUCCC – James researcher. "Inactivating BTK alone delayed CLL development in a mouse model, confirming that BTK is a clinically important target in CLL. This suggests that development of selective BTK inhibitors – in addition to multi-kinase inhibitors like ibrutinib – is reasonable in CLL."

To investigate the role of BTK in CLL, Johnson, Woyach and their colleagues used CLL cells from patients and two CLL mouse models, one of which spontaneously develops a malignancy very similar to human CLL. The researchers blocked BTK activity two ways: genetically and pharmacologically, using ibrutinib.

Key findings included:

- Inhibiting BTK expression in human CLL cells significantly decreased survival in tumor cells from 31 patients;
- A mouse model with inactive BTK due to a point mutation survived significantly longer than mice with active BTK (18.3 versus 13.2 months, respectively);
- In a mouse model of spontaneous CLL, animals treated with ibrutinib survived significantly longer than controls from the time of leukemia diagnosis (46 versus 24 days, respectively);
- In the same mouse model, treatment with ibrutinib significantly delayed leukemia onset compared with controls (10.7 versus 7.0 months) and extended overall survival (14.5 versus 12.3 months, respectively).

"Overall," Johnson says, "our findings validate BTK as a target for CLL therapy and strongly suggest that selective kinase-inhibitors might work in CLL like the drug imatinib does in chronic myeloid leukemia."

Provided by Ohio State University Medical Center