SOUTHWESTERN NEWS

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# UT SOUTHWESTERN RESEARCHERS LEARN LEUKEMIA DRUG MAY NOT TREAT CERTAIN FORMS OF DISEASE

DALLAS – Feb. 27, 2003 – A drug used to treat a rare form of leukemia may not fight the same disease in the central nervous system, according to researchers at UT Southwestern Medical Center at Dallas.

"The results were very unexpected," said Dr. Robert Ilaria Jr., assistant professor of internal medicine and molecular biology and senior author of the study that will appear in an upcoming issue of *Blood*. The study is now available online as a "First Edition Paper."

STI-571, also called Gleevec, was approved nearly two years ago by the Food and Drug Administration for the treatment of patients with chronic myelogenous leukemia (CML), a relatively uncommon leukemia, with about 5,000 new cases diagnosed each year in the United States. The drug blocks signals within cancer cells and prevents a series of chemical reactions that cause the cell to grow and divide.

Specifically, Gleevec is a chemical inhibitor of the Bcr/Abl tyrosine kinase, a dysregulated enzyme believed to cause leukemia. The drug prevents Bcr/Abl from stimulating the white blood cells to grow and overproduce, especially blast (immature) cells.

In the *Blood* study, Ilaria and his colleagues introduced Bcr/Abl into mouse bone-marrow cells to generate mice with a form of leukemia similar to human CML. Though not an inherited disease, CML has a genetic component. It is caused by an abnormal joining in bone-marrow cells of DNA sequences from two chromosomes that form an altered chromosome, called the Philadelphia chromosome, leading to an overproduction of white blood cells. CML usually develops slowly, although it can progress to a fast growing "accelerated phase."

When mice received Gleevec for treatment of CML, many of them became lame, developing altered posture, weak limbs and neurological abnormalities. These abnormalities were originally believed to be from drug toxicity, but further investigation revealed all the mice developed central-nervous-system (CNS) leukemia in their brain and spinal cord, Ilaria said. It was not related to their existing CML, which was responding well to treatment.

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Additional mice studied by the researchers showed the drug does not cross the blood-brain barrier, thereby allowing CNS leukemia to develop. Similar results also have been observed in nonhuman primates, and there has been one published case report of a human developing CNS leukemia while on Gleevec, Ilaria said.

"We were able to demonstrate that Gleevec penetrated poorly into the central nervous system, providing a sanctuary for leukemia cells to avoid being eradicated by the drug," Ilaria said. "At the time we submitted our work, this fact was not widely known.

"This tells us something about a drug that we did not really appreciate at the time. It's also a nice validation for the mice leukemia model and how it mimics many features of the human disease."

These results will be useful in the additional study of anti-CML drugs and in better defining the mechanisms for limited Gleevec penetration into the central nervous system, Ilaria said. Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) – notorious for being aggressive and incurable without a bone-marrow transplant – is the other form of leukemia that contains the altered chromosome, he said.

"So far in humans, it appears only CML cases that progress to lymphoid blast crisis (a marked increase in immature cells) or patients with Philadelphia chromosome-positive ALL are at-risk for CNS leukemia," Ilaria said. "Such patients will require CNS treatments with other chemotherapeutic drugs besides Gleevec."

The research was supported by the National Institutes of Health and the Leukemia Association of North Central Texas.

Other UT Southwestern contributors to the *Blood* study were Dr. James A. Richardson, professor of pathology and molecular biology, and Nicholas C. Wolff, first author of the study and research associate in the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research. A researcher from the University of Pittsburgh Cancer Institute also contributed to the work.

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