Finding key to cancer drug Gleevec's limitations

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University of Michigan researcher Theodora Ross wants to make Gleevec more potent against chronic myelogenous leukemia. Credit: University of Michigan

University of Michigan researchers have developed an animal model that provides strong evidence why imatinib, marketed as Gleevec, helps patients with chronic myeloid leukemia survive longer, but does not keep the disease from returning if treatment ends.

Leukemia-initiating cells are able to live below the drug's radar and enable the disease to recur in most cases after treatment stops, the researchers report in the August issue of *Cancer Cell*.

The researchers already are using their findings to test combinations of

imatinib and other drugs to find ways to sensitize the leukemia-initiating cells to imatinib and enhance its power.

Context

Imatinib, now the standard first-line treatment for chronic myeloid leukemia or CML, has prolonged lives, but does not keep many patients from eventually moving into the disease's later, more severe stages.

Until imatinib was introduced in 2001, people with CML faced a grim prognosis, with few surviving five years after diagnosis unless they received bone marrow transplants. Imatinib has reversed that prospect, allowing 95 percent of people with CML to survive five years.

Yet it soon became clear that the disease almost always returns without maintenance treatments of imatinib. Imatinib treatment cures the disease in at best 5 percent of cases. Maintenance treatments are a concern, because the drug can cause side effects such as extreme fatigue, nausea, diarrhea and muscle pain. These force 15 percent of cancer patients to stop taking imatinib; some then undergo bone marrow transplants, the only treatment known to cure CML.

Imatinib, one of several targeted cancer therapies developed in recent years, inhibits certain enzymes associated with mutated genes that are involved in CML. Cancer researchers have suspected - but have not known until now - that certain cells that set events in motion toward CML are able to resist the drug.

"The mouse model we have developed for CML allows us to identify, understand and target the tumorigenic cell," says Theodora Ross, M.D., Ph.D., associate professor of internal medicine at U-M and senior author of the study. Developing a mouse model that closely reproduces the progression of human CML was a 10-year process.

CML is a slowly progressing disease in which too many of certain white blood cells are made in the bone marrow. It is also called chronic granulocytic leukemia or chronic myelogenous leukemia. An estimated 5,050 men and women will be diagnosed with chronic myeloid leukemia in 2009, and 470 will die of the disease, according to the National Cancer Institute.

Implications

Ross says that the study findings point to a new goal in CML treatment: to find ways to make imatinib specifically kill the leukemia-initiating cells that at present remain unaffected by the drug.

She and her team are currently testing several two-drug combinations using their mouse model. Imatinib is being combined either with interferon, rapamycin (also known as sirolimus), arsenic or GM-CSF (marketed as Neupogen). They hope to find combinations that will make the initiating cells more vulnerable to imatinib's action. If successful in mice, the combined therapy eventually can be tested in people.

More information: Cancer *Cell*, Vol. 16, Issue 2, Aug. 4, 2009

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