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Gleevec holds potential as first drug to successfully treat neurofibromatosis

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Researchers at the Indiana University School of Medicine report that the anti-cancer drug Gleevec holds out promise to become the first effective treatment for neurofibromatosis, a genetic disease that has resisted treatments until now.

The research team is conducting clinical tests of the drug following successful laboratory tests and a "compassionate use" of the drug that showed dramatic results in a three-year-old girl at Riley Hospital for Children in Indianapolis.

Neurofibromatosis results from mutations in a gene called NF1, which causes tumors to form in the cells that make up the protective sheaths around nerves. In humans, NF1 mutations resulting in neurofibromatosis occur in one in 3,500 births, equally affecting both sexes and all races and ethnicities. It is the most common genetic disease in humans that results in a predisposition to cancer.

IU researchers have begun a phase 2 clinical test of Gleevec, treating neurofibromatosis patients with plexiform neurofibromas, which affect about 40 percent of people with neurofibromatosis. Such tumors often have a severe impact on patients' quality of life and can be fatal. They do not respond to chemotherapy drugs and are difficult or impossible to remove surgically.

"We are very hopeful about the potential of this drug and related therapies. There are no other therapies for these tumors. These patients

often suffer for years; they sometimes die from these tumors. These are very slow growing tumors that impair people's everyday lives," said D. Wade Clapp, M.D., Freida and Albrecht Kipp Professor of Pediatrics at IU School of Medicine.

The researchers report in the Oct. 31 issue of the journal *Cell* that the mutated nervous system cells, while still in a pre-tumor state, use molecular signals to recruit inflammatory system cells from the bone marrow to the vicinity of the nerve cells. Those inflammatory system cells – called mast cells – then are put to work helping create the cellular "scaffolding" and blood vessels necessary for the cancerous tumors to form.

The tumorigenic cells use a signaling system protein called c-kit to recruit the mast cells, making Gleevec an attractive treatment candidate because it acts on the c-kit molecule, said the researchers, who include Feng-Chun Yang, M.D., Ph.D., assistant professor of pediatrics, David A. Ingram Jr., M.D., associate professor of pediatrics, and Luis F. Parada, Ph.D., professor of developmental biology at the University of Texas Southwestern Medical Center.

The researchers discovered that while both copies of the NF1 gene in the nervous system cells must be mutated in order for tumors to form, those mutations alone are not sufficient. Tumor growth is enabled by additional NF1 mutations in nearby cells – most likely the mast cells. However, unlike the nerve cells, where both NF1 genes are mutated, only one of the mast cell NF1 genes needs to be mutated for tumor growth to begin.

While the research was being conducted in animal models, a critically ill three-year-old patient presented at Riley Hospital for Children with a plexiform neurofibroma that was compressing her airway. With Gleevec administered under a compassionate use protocol, the patient's tumor

was reduced by about 80 percent, Dr. Clapp said. The patient was subsequently removed from treatment and is being followed, he said.

Because Gleevec is already an FDA- approved drug used to treat chronic myeloid leukemia and several other types of cancer, the human testing for NF1 will not need to begin with safety testing.

"Patients taking Gleevec for chronic myeloid leukemia have often been taking it for 10 to 15 years without major consequences, and live a normal life. It's a very good, very well tolerated drug," Dr. Clapp said.

Researchers expect to enroll about 40 patients, ranging from age three to adults, in the clinical trial.

Source: Indiana University