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Group of rare blood cancers respond to new treatment pioneered by Stanford physician

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A global trial of an oral medication called midostaurin indicates that the drug can produce partial or complete resolution of organ damage in 60 percent of patients with a group of rare blood cancers known collectively as advanced systemic mastocytosis.

The results of the open-label, phase-2 trial will be published June 30 in the *New England Journal of Medicine*. Jason Gotlib, MD, an associate professor of medicine at the Stanford University School of Medicine, led a team of international investigators that conducted the study, which enrolled 116 patients at 29 sites around the world. The study was funded by Novartis Inc., which manufactures midostaurin, also known as PKC412.

"Few patients with advanced systemic mastocytosis respond to the currently available drugs," said Gotlib. "They desperately need an alternative treatment. We are very hopeful that midostaurin will soon be approved by the FDA for this rare disease." Patients with advanced SM have a poor prognosis, with an expected life span of less than six months to 3.5 years, depending on the disease subtype.

Gotlib is the lead author of the study; Andreas Reiter, MD, of the University of Heidelberg, is the senior author.

Proliferation of mast cells

Systemic mastocytosis is caused by the abnormal accumulation of a type of white blood cell called a mast cell in the bone marrow, spleen, liver, lymph nodes, skin and gut. These cells mediate the body's allergic and inflammatory responses and play a role in defending the body against bacteria, fungi and viruses. Patients with systemic mastocytosis can experience flushing, itching, diarrhea and, in some cases, anaphylaxis, when the mast cells release inflammatory mediators such as histamine. In advanced forms of the disease, the infiltration of organs by the mast cells leads to low blood counts and liver function abnormalities as well as malabsorption and weight loss.

About 90 percent of patients with advanced SM have a particular mutation known as D816V in the gene that encodes a protein called KIT that controls the growth of mast cells. KIT is a member of a class of proteins called tyrosine kinases that modulate the activity of many signaling pathways within a cell. Mutations that cause kinases to be "always on" are responsible for many types of cancers, including advanced SM. Drugs known as protein kinase inhibitors are often used to block the activity of the mutated kinases in order to slow or stop disease progression.

However, the only currently approved treatment for advanced SM, a kinase inhibitor marketed by Novartis as imatinib, or Gleevec, is not active against the KIT protein with the D816V mutation—leaving most patients without an effective treatment.

Lack of options motivates researcher

Gotlib, a hematologist, pioneered the testing of midostaurin for advanced SM after becoming frustrated with the lack of treatment options.

In 2002, as a hematology fellow at Stanford, he treated a patient who

was severely ill with another type of blood cancer caused by a mutated tyrosine kinase. The patient initially responded to imatinib, but developed another mutation in his cancer cells within a few months that led to resistance to the drug. Although Gotlib was unable to save that patient, the experience remained with him.

Shortly thereafter, researchers at Harvard showed that the imatinib-resistant cancer that Gotlib's patient developed could be overcome by midostaurin in a mouse model of the disease.

"I wondered if midostaurin could work for other patients resistant to imatinib," Gotlib said. He realized that advanced SM might be a good disease in which to test the drug, given that the majority of patients suffering from it carry the mutated KIT D816V protein resistant to imatinib.

'A dramatic response'

"I didn't have any patients with advanced SM at the time, but another physician in my division was treating someone with mast cell leukemia, a highly fatal variant of systemic mastocytosis," Gotlib said. He convinced Novartis to allow him to give the patient midostaurin under the company's compassionate-use program. "We saw a dramatic response. The patient, who was near death, improved enough to be released from the hospital, go home and begin cooking meals again."

Although the patient's disease was controlled for only a few months, the experience established the potential activity of midostaurin in advanced SM. As a result, Gotlib, along with colleagues from Stanford and elsewhere, initiated further trials of midostaurin in the United States in 2005, as well as the current, international trial, which was launched in 2009.

Study findings

Sixty percent of patients in the current trial experienced complete or partial resolution of organ damage related to the disease. As a result, responding patients were less likely to need red blood cell or platelet transfusions and they experienced improvements in liver function and fewer signs of malabsorption such as weight loss.

Patients treated with midostaurin who experienced improvement in organ damage or a significant decrease in the percentage of abnormal mast cells in the bone marrow survived significantly longer than those who did not demonstrate these responses. The median overall survival of patients was 28.7 months. The survival benefit among patients with a severe subtype of the disease called mast cell leukemia was particularly striking, according to Gotlib. Although most people succumb to this form of the disease within six months of diagnosis, the median overall survival of all midostaurin-treated mast cell leukemia patients was 9.4 months.

Of 39 patients whose spleen size was evaluated, nearly 80 percent saw a reduction in the enlargement that is a common feature of advanced SM that contributes to abdominal pain and decreased appetite.

The most frequent side effects of midostaurin were low-grade nausea, vomiting and diarrhea, which were usually responsive to administration of the drug with meals and anti-nausea medicines. Patients otherwise reported a significant improvement in disease-related symptoms and quality of life.

Midostaurin is currently available on a compassionate-use basis for patients with advanced SM. Gotlib said the investigators hope to evaluate its use in earlier-stage patients whose disease is unresponsive to conventional clinical approaches or to prepare more advanced-stage

patients for a bone marrow transplant in an attempt to cure the disease.

"This is an evolution of a treatment that originated in 2002 with a patient with an entirely different disease," Gotlib said. "We hypothesized that midostaurin might work for patients with advanced SM, and that led to a case report and ultimately the current international trial. Our study represents more than a decade of work and collaboration between academia, the pharmaceutical industry, and the SM patient community, and we are very hopeful that it will lead to approval of a new treatment for this rare, devastating disease."

Provided by Stanford University Medical Center

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