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Drug offers relief for symptoms of myelofibrosis

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People with a blood cancer — myelofibrosis — can benefit from a drug called ruxolitinib, according to a randomized, double-blind, placebo-controlled clinical trial that included patients and researchers from the Stanford University School of Medicine. The results of the multi-site phase-3 trial, which will be published in the March 1 issue of the *New England Journal of Medicine*, led the Food and Drug Administration to approve the drug in November as treatment for people with intermediate or advanced cases of the disease.

Ruxolitinib is marketed as Jakafi by Incyte Corp., which funded the trial, known as COMFORT-1. Investigators at the MD Anderson Cancer Center in Houston and the Mayo Clinic in Scottsdale, Ariz., led the study. The Stanford arm of the trial was managed by Jason Gotlib, MD, MS, associate professor of medicine. More than 300 patients at 89 clinical sites participated in the trial.

"Patients with myelofibrosis have a quality of life that is severely impaired," said Gotlib, who treats between 50 and 75 newly diagnosed people each year in his Stanford clinic. Fifteen of his patients participated in the study, making Stanford the single largest recruiting site.

Individuals with advanced forms of myelofibrosis develop worsening blood counts, spleen enlargement and other symptoms including fever, night sweats and pain in their bones and muscles. "With massive splenomegaly, patients develop abdominal discomfort, early satiety and

weight loss," said Gotlib. In the study, many patients who received the drug experienced a significant reduction in spleen volume and a lessening of symptoms.

Hagop Kantarjian, MD, chair of the department of leukemia in the division of cancer medicine at MD Anderson Cancer Center, is the senior author. The first author is Srdan Verstovsek, MD, PhD, an associate professor in the same department at MD Anderson.

"Our clinical experience indicates that ruxolitinib is clearly better at relieving patients' symptoms and quality of life than anything we could offer them before," said Gotlib. A parallel phase-3 randomized trial named COMFORT-2, which was conducted in Europe, demonstrated that ruxolitinib was also superior to the best available therapy in reducing spleen size and disease-related symptoms.

Myelofibrosis belongs to a class of diseases known as myeloproliferative neoplasms, or MPNs, that affect about 150,000 people in this country. About 30,000 of these have myelofibrosis. MPNs occur when the bone marrow begins to overproduce red blood cells, platelets or white blood cells. In myelofibrosis, the abnormal proliferation of these cells leads to extensive scarring within the bone marrow, making it less effective at making blood for the body. As a result, the body moves blood production to the spleen and liver, which become enlarged as they try to compensate for the underperforming marrow. People with MPNs can develop life-threatening blood clots and bleeding, and in some cases their condition progresses to acute leukemia. Some MPNs respond well to current treatments, but myelofibrosis does not.

Although myelofibrosis typically progresses slowly, patients often exhibit an inexorable course resulting in premature death. The overall survival ranges from 11 years in low-risk patients to a little more than two years in patients with high-risk disease. Stem cell transplantation can

cure some patients, but it is available to only a small proportion of patients and can carry substantial treatment-related morbidity and mortality.

Ruxolitinib is the first FDA-approved therapy for the disorder, and the first of a class of compounds called JAK2 inhibitors. This targeted therapy was developed to block the action of the JAK2 tyrosine kinase protein, which is mutated and abnormally active in 50-60 percent of myelofibrosis cases. However, for reasons that are not entirely understood, the drug works in patients regardless of whether they have the mutant protein.

In the trial, patients were randomly assigned to receive either ruxolitinib (155 patients) or a placebo (154 patients) orally twice a day. Their spleen volumes were monitored over the course of the 24-week study by magnetic resonance imaging, and patients reported their symptoms using an electronic diary. The primary endpoint in the study was a 35 percent reduction in spleen volume.

"It quickly became apparent who was getting the placebo and who was getting the drug," said Gotlib, noting that the spleen volume in people receiving the drug began to decrease within one to two weeks. All told, 41.9 percent of patients on the drug met the study endpoint of at least a 35 percent reduction in spleen volume, while only 0.7 percent of those on the placebo did so. Patients receiving placebo were allowed to crossover to active, unblinded treatment with ruxolitinib after a designated period of time.

Nearly 46 percent of patients on ruxolitinib reported an improvement of 50 percent or more in their disease-associated symptoms, versus about 5 percent of those on placebo. The drug did have some side effects, however, including anemia. And although the majority patients maintained a smaller spleen volume for at least 48 weeks while on the

drug, their spleens began to enlarge again if they stopped taking the drug.

"Ruxolitinib doesn't cure the disease," said Gotlib, "but the degree of benefit is clinically meaningful and substantial, and allows many patients to re-engage in their daily activities."

Compared with placebo, ruxolitinib therapy was associated with a 50 percent reduction in mortality after nearly one year of follow-up, but Gotlib indicated that the long-term implications of these data are not clear. He believes that the FDA approval of ruxolitinib and the ongoing evaluation of other JAK inhibitors in clinical trials will continue to spur drug development for myelofibrosis and similar orphan diseases for which there is a large unmet need. Ruxolitinib is now being evaluated in clinical trials of other MPNs.

Provided by Stanford University Medical Center