JAK inhibitor provides rapid, durable relief for myelofibrosis patients

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An oral medication produces significant and lasting relief for patients with myelofibrosis, a debilitating and lethal bone marrow disorder, researchers at The University of Texas MD Anderson Cancer Center report in the Sept. 16 *New England Journal of Medicine*.

Myelofibrosis is caused by the accumulation of malignant bone marrow cells that trigger an inflammatory response, scarring the bone marrow and limiting its ability to produce blood, causing anemia.

"The problem with myelofibrosis is the lack of available therapies for patients - there are none approved for this disease today," said principal investigator Srdan Verstovsek, M.D., Ph.D., associate professor in M. D. Anderson's Department of Leukemia. Average life expectancy for people with this disease is 5 to 7 years. Available therapies approved for other diseases provide little response and are mainly palliative.

"This experimental drug is the first to target one of the underlying abnormalities in the malignant cells that cause myelofibrosis," Verstovsek said. "It provides unprecedented reduction of enlarged spleens that are a central characteristic of the disease, and relieves pain, fatigue and other symptoms, improving quality of life."

Swollen spleens cause pain, malnutrition

"Interestingly, other organs, mainly the spleen, attempt to take over the

production of blood cells. Bone marrow forms in the spleen," Verstovsek said. Malignant cells also accumulate there. "The growing spleen causes significant problems for the patient, and not just because it's painful. It compresses the stomach and bowels, so patients suffer malnutrition and lose weight. The ability to walk and to bend is affected, and the body deteriorates overall."

End-stage patients resemble the severely malnourished, with bloated abdomens and thin limbs. Patients on the study gained weight while on the medication.

The phase I/II clinical trial of INCB018424, a JAK1 and JAK2 inhibitor developed by Incyte Corp., established maximum tolerated doses and then optimal dosing regimens for the drug, which targets abnormal signaling caused by a specific mutation in the JAK2 gene that was discovered in 2005 in patients with myelofibrosis.

The clinical trial began in June 2007 at MD Anderson and the Mayo Clinic and enrolled 153 patients, all of whom had either advanced disease or were newly diagnosed with high intermediate- or high-risk myelofibrosis. Clinical responses have been maintained and 115 patients (75 percent) remain on the trial.

Most patients benefited, with those on optimal doses experiencing:

- A median reduction in spleen volume, as measured by magnetic resonance imaging, of 33 percent at six months, with 48 percent enjoying reductions of 35 percent or higher. This equals a median reduction of 52 percent in the length of the spleen below the ribcage, measured by palpation, which is how spleen size is typically measured in clinical practice.

- Swift and lasting spleen reduction; 70 percent to 82 percent of patients on the three optimal dosing regimens had spleen reduction of at least 25 percent that occurred within the first two months of therapy and lasted beyond a year.

- Rapid and lasting improvement in symptom score, with 51 percent of patients achieving a 50 percent reduction at one month, and 58 percent maintaining that reduction at six months.

- Greater exercise capacity as measured in a six-minute walk. Patients increased their distance by a median of 34 meters at one month and 71 meters at six months.

- Median weight gain ranging from 14.5 pounds to 20.6 lbs after one year.

Symptom improvement coincided with a quick and sustained reduction in a variety of inflammatory cytokines involved in disease biology.

The main side effect is lowered blood cell counts in some patients, which can be remedied by lower doses or temporarily halting therapy.

"The JAK2V617F mutation is one of several involved in myelofibrosis. It's the most prevalent, found in about half of patients. But it's not the sole cause of the disease," Verstovsek noted. "Myelofibrosis is too complex to be eliminated by a single drug. It will probably take combination therapies to cure it."

Normally, JAK2 is turned on by various growth factors to make new blood cells as needed. The JAK2V617F mutation leaves the JAK2 enzyme permanently turned on, which causes the overgrowth of bone marrow cells at the heart of myelofibrosis.

While the JAK2 inhibitor was expected to help patients with JAK2 mutations, the drug worked whether they had the mutation or not. "This suggests that patients who do not have specific mutations still have a very active JAK signaling pathway and can benefit from JAK inhibition," Verstovsek said. "However, because the drug also inhibits normal JAK2, it can lead to low blood counts that can limit dosing."

Provided by University of Texas M. D. Anderson Cancer Center