JAK2 inhibitor demonstrates effective, durable control of myelofibrosis

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A first-in-its class oral medication provides significant and durable relief for patients with a rare, debilitating and lethal bone marrow disorder called myelofibrosis, researchers at The University of Texas M. D. Anderson Cancer Center reported today at the 51st Annual Meeting of the American Society of Hematology.

"Until now, we have never been able to target an abnormal signaling pathway in the malignant cells that cause myelofibrosis, a disease for which there is no approved therapy at all," said principal investigator Srdan Verstovsek, M.D., Ph.D., associate professor in M. D. Anderson's Department of Leukemia. Average life expectancy is 5 to 7 years. Available therapies offer mainly palliative care.

The phase I/II clinical trial of INCB018424, a JAK1 and JAK2 inhibitor, targets the abnormal signaling caused by JAK2V617F mutation in the JAK2 gene, which was discovered in patients with myelofibrosis and similar myeloproliferative diseases in 2005.

"This drug provided unprecedented reduction of enlarged spleens and improvement in quality of life, with patients gaining weight, experiencing less pain and enjoying increased exercise capacity," Verstovsek said.

"Myelofibrosis is caused by the accumulation of malignant cells that results in extensive scarring in the bone marrow and limits blood production, causing anemia. The spleen and other organs attempt to take

over the production of blood cells," Verstovsek said, "which causes massive swelling of the spleen. Patients have a poor quality of life, with fatigue, weight loss, abdominal, bone and muscle pain, night sweats and sometimes severe itching. End-stage patients resemble the severely malnourished, with bloated abdomens and thin limbs."

The trial of the experimental JAK2 inhibitor INCB018424 (424) began in June 2007 and enrolled 153 patients. Clinical responses have been maintained over the course of treatment and 115 patients remain on the trial.

Spleen size, a symptom score based on patient surveys, and a six-minute walk that gauged exercise capacity, were used to evaluate response to the drug. All patients benefited, and those on an optimized dose of the drug experienced:

- 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.

- 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 50 percent reduction at six months.

- Added distance to their six-minute walk by a median of 33 meters at one month and 70 meters at six months.

Additional analysis showed that spleen shrinkage was associated with greater improvements in symptom score, exercise capacity and fatigue.

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

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

"JAK2V617F mutation is one of several mutations involved in myelofibrosis and is the most prevalent mutation, 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."

"This medication is designed to address underlying abnormalities in myelofibrosis and it does allow us to control the disease very well in most patients," Verstovsek said. "However, it will probably take combination therapies to cure myelofibrosis."

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 originally thought to be aimed at patients with JAK2 mutations, the drug helps patients 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."

Source: University of Texas M. D. Anderson Cancer Center (news : web)