Combination therapy using JAK2 and HSP90 inhibitors increased efficacy in myelofibrosis in vivo

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Researchers have demonstrated that combination therapy with PU-H71 and ruxolitinib increases the durability and effectiveness of a treatment that had previously shown limited utility for patients with myelofibrosis.

Myelofibrosis is a chronic malignant blood disorder commonly caused by mutations in the JAK2 pathway (which normally signals the body to create blood cells), including most commonly the JAK2 V617F mutation. This mutation leads to the overproduction of scar tissue in the bone marrow and shifts red and white blood cells and platelets from the bone marrow into the spleen and liver, enlarging the organs and leading to anemia, infection, inflammation, and easy bleeding and bruising.

The first approved treatment for myelofibrosis is ruxolitinib, a therapy that targets the JAK2 mutation by blocking the action of all JAK-related genes in the body, including those from both healthy and diseased cells. However, clinical results have been modest to date. In particular, resistance to JAK inhibitors has been associated with an increase in JAK2 levels, which leads to continued JAK2 activity despite ruxolitinib treatment. This resistance can be reversed by inhibiting heat shock protein 90 (HSP 90), which destabilizes JAK2 and reduces JAK2 protein levels. Since cancer cells are continually dividing, they constantly burden the cell system and depend on HSP90 function to allow the JAK2 protein to maintain cancer cells' function and growth.

Recognizing HSPs as a potential target for treatment, researchers have recently explored the possibility of blocking HSP90 to treat blood cancers. Unlike ruxolitinib, which blocks the function of the abnormal JAK2 protein that maintains the function of the cancerous cell, HSP90 inhibitors block the function of HSP90 in the cells. This allows for the breakdown of the JAK2 protein and weakens the cell's ability to grow and divide, allowing it to become sensitive to treatment. PU-H71, a HSP90 inhibitor, previously shown to have efficacy in different cancer cells and animal models including myelofibrosis, is currently undergoing Phase I clinical trials.

One emerging hypothesis is that combining the JAK2 inhibitor ruxolitinib with HSP90 inhibitors may increase the efficacy of myelofibrosis treatment. To test this hypothesis, a team of investigators treated mice that had myelofibrosis with the investigational combination therapy, comparing their results to control groups treated with ruxolitinib alone or PU-H71 alone. They also assessed the effects of adding PU-H71 treatment as a second therapy to mice already being treated with ruxolitinib. Study endpoints included reduction in white blood cell count, platelet count, and spleen weight; reduction in JAK2 protein levels in the blood, spleen, and bone marrow; and presence of scar tissue in the bone marrow.

In this study, researchers observed that mice that had been treated with the combination therapy had a more significant reduction in white blood cell count, platelet count, and spleen weight after 14 days of therapy. The benefits of combination therapy versus ruxolitinib alone were even more significant after 29 days of treatment. The combination therapy was also associated with a reduction in bone marrow scar tissue and a reduction in the activity of the JAK2 pathway. Comparable effects were also observed in mice that were treated with PU-H71 plus ruxolitinib after initial monotherapy with ruxolitinib, further demonstrating the efficacy of combination treatment. Most importantly, in those mice

treated with combination ruxolitinib and PU-H71 therapy, investigators observed a decrease in JAK2 levels, revealing that PU-H71 may prevent or reverse the increases in JAK2 protein levels seen with chronic ruxolitinib therapy. Of note, combination treatment was well tolerated and not associated with increased side effects compared to either therapy alone.

"Now that we have found a way to combat the treatment resistance commonly seen in myelofibrosis, we are continuing these trials with the hope that these results will one day provide a treatment option superior to what is currently available for these patients," said Priya Koppikar, PhD, second author and research scholar in the Human Oncology and Pathogenesis Program (HOPP) at Memorial Sloan-Kettering Cancer Center in New York.

"We believe these results provide the impetus for the first studies combining ruxolitinib with HSP90 inhibitors in myelofibrosis patients, and we are working to begin these trials as soon as possible to improve their outcomes," added Ross Levine, MD, lead author and Associate Attending Physician in the HOPP and Leukemia Service at Memorial Sloan-Kettering Cancer Center in New York.

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