Small molecule may disarm enemy of cancer-fighting p53

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A pioneering clinical trial is testing the effectiveness in leukemia of a small molecule that shuts down MDM2, a protein that can disable the well-known tumor suppressor p53.

Michael Andreeff, M.D., Ph.D., professor of Medicine and chief of Molecular Hematology and Therapy in the Department of Leukemia at The University of Texas MD Anderson Cancer Center, presented preliminary results of this ongoing Phase I study at the 52nd Annual Meeting of the American Society of Hematology. The clinical trial is under way at MD Anderson and five other sites in the United States and United Kingdom.

The first-in-class drug has shown clinical activity in some patients and been well-tolerated, Andreeff said.

Andreeff has been researching the interaction between MDM2 and p53 for five years. He says he believes this study may lead to an effective new way to fight some types of cancer with fewer side effects.

"P53 can be activated by chemotherapy or radiation, but both of these therapies carry risks of causing secondary tumors," he said. "If we can activate this tumor-suppressor with a method that is non-genotoxic and does not cause damage to a patient's DNA, we may be able to help avoid secondary tumors caused by other treatments."

Too much MDM2 degrades p53

Normally, p53 halts the division of defective cells and forces them to commit suicide or lose the ability to reproduce. However, the tumor suppressor is disabled in many types of cancer, often because of gene mutations or defective signaling.

While mutations of the TP53 gene are rare in cancers of the blood, the p53 protein may be degraded by other factors, including high levels of MDM2, which binds to p53 and orchestrates its degradation.

Previous research has suggested that p53 activation by disrupting the binding of MDM2 to p53 may be a novel strategy for cancer therapy. In preclinical studies, small-molecule MDM2 antagonists called Nutlins were found to be effective in solid tumors, leukemia and lymphoma.

The drug used in this study, RG7112, a novel small molecule being developed by Roche, is a member of the Nutlin family.

Clinical effects seen

Patients with relapsed or refractory acute or chronic leukemia were given RG7112 orally each day for 10 days, followed by 18 days of rest. Forty-seven patients, including 27 with acute myeloid leukemia (AML), have been treated to date.

There has been evidence of clinical activity, and one patient with AML has been leukemia-free for nine months. Reductions in lymph node and spleen size, as well as in circulating leukemia cells, were seen in chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

"RG7112 has been well tolerated, and we've seen some effectiveness,"

Andreeff said. "So far it has done exactly what we thought it would. This gives us evidence it can be used in patients, is well-tolerated and can be given in dosages that can escalate to a point that shows a higher response rate."

Next steps

Enrollment in this study is ongoing and will be updated. Future single-agent and combination studies of RG7112 in leukemias are planned.

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