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Cancer metabolism drug AG-221 shows clinical activity in advanced blood cancers

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AG-221, a novel inhibitor of isocitrate dehydrogenase (IDH) 2-mutant metabolic enzyme, was well tolerated and showed early promise in patients with advanced and refractory blood cancers harboring IDH2 mutations, according to the initial results of a phase I study presented here at the AACR Annual Meeting 2014, April 5-9.

Mutations in the genes for the metabolic enzymes IDH1 and IDH2 are thought to be the drivers of distinct subsets of acute myeloid leukemias (AML)," said Eytan M. Stein, M.D., assistant attending physician in the Leukemia Service at Memorial Sloan Kettering Cancer Center in New York. "They lead to the production of increased levels of an oncometabolite called 2-hydroxyglutarate (2-HG), which is hypothesized to prevent normal healthy bone marrow cells from maturing, leading to cancer.

"AG-221 is a novel compound that blocks the mutated IDH2 enzyme and decreases the levels of 2-HG, thus allowing the immature bone marrow cancer cells to mature and differentiate normally," explained Stein. "Although the primary goal of this phase I study was to determine the safety and tolerability of AG-221, we were pleased to find promising clinical activity in patients whose AML had IDH2 mutations, even at the lowest drug dose we tested."

In the reported portion of this dose-escalation, phase I trial, Stein and colleagues recruited 21 patients who had AML and one patient who had myelodysplastic syndrome. All patients tested positive for IDH2

mutations. Patients were recruited to four cohorts to receive AG-221 orally at dosages of 30 mg twice daily, 50 mg twice daily, 75 mg twice daily, or 100 mg once daily.

The clinical activity reported here was from the first two cohorts, which enrolled 10 patients with AML who had received one to four prior treatments. Their blood cancers had two types of IDH2 mutations: R140Q was found in eight patients, and R172K was found in two.

Following treatment with AG-221, six of seven evaluable patients had objective responses which are ongoing, including three who had a complete remission and two who had a complete remission with incomplete platelet recovery. Three patients were not evaluable due to disease-related sepsis. The investigators continue to enroll patients to receive higher doses of AG-221, and the maximum tolerated dose has not been reached yet, according to Stein.

They performed pharmacodynamic evaluations in the responding patients' blood and found evidence of drug uptake. They also found a greater than 90 percent reduction in the levels of 2-HG, providing proof-of-principle for the drug's mechanism of action. In addition, they found evidence of maturation of the bone marrow cancer cells in these patients' blood with normalization of blood counts, consistent with the clinical responses observed.

The investigators noted that the drug was generally well tolerated. Severe drug-related adverse events included an abnormally high white blood count and confusion in one patient each.

One of the two patients who had complete remission was removed from the study for further management with a bone marrow transplant. The remaining five responding patients continue to receive AG-221, according to Stein.

"Currently, for patients with AML, especially for those who are over 60 years of age, the overall survival rate is between 5 and 10 percent with traditional therapies," said Stein. "The early data from this trial showing clinical activity of AG-221 are encouraging and provide early validation for IDH2 as a promising cancer target in blood cancers. We look forward to additional updates as the study progresses. If patients with AML harboring IDH2 mutations can be successfully treated with AG-221, it could significantly improve their quality of life."

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