MedicalXpress

Ponatinib acts against the most resistant types of chronic myeloid leukemia

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A previously invincible mutation in chronic myeloid leukemia (CML) has been thwarted by an investigational drug in a phase I clinical trial reported in the current edition of The *New England Journal of Medicine*.

All 12 patients in the trial with chronic phase CML and the T315I mutation had a complete hematologic response (absence of CML cells in the blood) after treatment with ponatinib. Eleven had a major reduction in CML cells in the bone marrow and nine achieved a complete cytogenetic response – no cells in the marrow.

T315I is present in up to 20 percent of patients and blocks the docking station where three other successful CML drugs normally connect to the mutant protein.

Ponatinib also induced high response rates among the broader group of patients who had mutations other than T315I or no detectable mutations. Among 65 patients with relapsed or resistant CML at varying stages of the disease or with Philadelphia-chromosome positive acute lymphoblastic leukemia (ALL), 67 percent with other mutations and 46 percent with no mutations achieved a complete cytogenetic response.

"Ponatinib is a promising new treatment for patients who have run out of options and its activity against other resistant mutations and in patients with no known mutations suggests a broad range of efficacy for this drug," said trial principal investigator Jorge Cortes, M.D., professor in The University of Texas MD Anderson Department of Leukemia.

Cortes will report the results of a pivotal phase II clinical trial of ponatinib at the 54th ASH Annual Meeting and Exposition in December.

The U.S. Food and Drug Administration in October accepted a new drug application by ARIAD Pharmaceuticals for accelerated review of ponatinib for patients with resistant or intolerant CML or Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL).

Targeted therapy success story

CML is caused by the abnormal gene BCR-ABL, which occurs when two chromosomes swap portions of their DNA from the BCR and ABL genes during cell division. This abnormality is called the Philadelphia chromosome and the resultant BCR-ABL fusion protein drives the overproduction of white blood cells that characterizes CML. BCR-ABL is a tyrosine kinase, a type of protein that acts as an on-off switch by attaching a phosphate group to other proteins.

Discovery of the drug imatinib (Gleevec) revolutionized treatment of CML. Now approximately 90 percent of patients survive for at least five years, up from about 50 percent before imatinib. Two second-generation drugs, nilotinib (Tasigna) and dasatinib (Sprycel) are more potent than imatinib. Each can be used in frontline therapy.

"Imatinib is a terrific drug, however 30-40 percent of CML patients become resistant to it," Cortes said. "Nilotinib and dasatinib work for 40-50 percent of these patients."

Preclinical experiments indicated ponatinib acts against BCR-ABL and all known mutant forms of the protein.

Ponatinib active against known mutations and no

mutations

The phase I trial enrolled 81 patients with blood cancers at five centers, 60 with CML and five with Philadelphia Chromosome-positive ALL. The patients had relapsed or resistant disease and 91 percent had been treated with at least two of the approved drugs. Median follow-up was 56 weeks.

- Among 43 chronic phase CML patients, 42 had complete hematological response, 31 (72 percent) had a major cytogenetic response, 27 (63 percent) had a complete cytogenetic response (no CML cells in the bone marrow) and 19 (44 percent) achieved major molecular responses.
- Duration of response for chronic phase patients with major cytogenetic response ranged from 8 to 117 weeks, with median duration yet to be reached.
- Patients treated within 0 to 5 years of diagnosis had better response rates than those treated with ponatinib 5 to 24 years after diagnosis.
- More than 60 percent of the 15 patients in chronic phase CML with non-T315I mutations and 13 with no detectable mutations achieved a major cytogenetic response.
- All 12 of the chronic phase CML patients with T315I remained on the study at the time of analysis.
- Of 22 patients with advanced CML (accelerated or blast stages) eight had a major hematological response, seven a major cytogenetic response and two a major molecular response.
- Seven patients had advanced CML and the T315I mutation. Two achieved major hematologic response, two major cytogenetic responses and two major molecular responses.

The dose escalation trial started at a daily oral dose of ponatinib of 2 mg

ranging up to 60 mg. The investigators settled on a 45mg dose.

The most common non-hematologic side effects were skin disorders, fatigue and nausea at the lower grade 1 or 2 levels. Pancreatitis occurred in 11 patients and was a serious adverse event in eight. Nine of the 11 experienced one episode of pancreatitis, only two discontinued treatment.

Twelve patients with acute myeloid leukemia also participated in the trial. A separate paper will address those results.

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