MedicalXpress

Phase I trial indicates ponatinib may thwart most resistant CML

December 6 2010

A new drug appears to help chronic myeloid leukemia patients who are out of treatment options after first- and second-line drugs have failed them or because their cancer cells have a mutation that makes them resistant from the start, researchers reported at the 52nd Annual Meeting of the American Society of Hematology.

In a Phase I clinical trial, the drug ponatinib produced major or complete hematologic responses (absence of CML cells in the blood) and cytogenetic responses (absence of leukemia cells in the bone marrow) among two groups of patients:

- Those who have tried two or three of the drugs that have revolutionized treatment of CML – imatinib (Gleevec), nilotinib (Tasigna) and dasatinib (Sprycel) – and developed resistance to them.
- And those whose leukemia cells carry the T315I mutation, which resists all current therapies.

"Ponatinib seems to be filling the gap we had for patients who right now have no good treatments left," said Jorge Cortes, M.D., professor in The University of Texas MD Anderson Cancer Center Department of Leukemia, who presented the group's findings. "We are very encouraged by such strong results in the Phase I setting and have begun a pivotal Phase II clinical trial."

Preclinical research had indicated that ponatinib, developed by ARIAD Pharmaceuticals, inhibits all mutations that cause resistance to drugs that stifle the BCR-ABL protein which drives CML. BCR-ABL is produced by the aberrant gene bcr-abl, which occurs when two chromosomes swap portions of their DNA from separate bcr and abl genes. The abnormality is called the Philadelphia chromosome.

As of July 2010, 67 patients were enrolled in the study: 57 with CML, including 42 in the chronic, or early, stage, seven in the accelerated stage and eight in the blast phase, the most advanced form of the disease. Three had Philadelphia-positive acute lymphoblastic leukemia, three had acute myeloid leukemia and four were divided among other blood malignancies.

A total of 48 patients were evaluable at the time of reporting. Of these:

- 30 of 32 patients (94 percent) in CML chronic phase had complete hematologic responses; 20 (63 percent) had major cytological responses, 12 complete and eight partial. Of these 20 cytogenetic responders, 18 remained on the treatment with no disease progression.

- All 11 chronic phase CML patients who had the T315I mutation had complete hematologic response and nine had major cytogenetic responses, eight of which were complete.

- For 16 CML patients in accelerated or blast phase or with Philadelphia-positive acute lymphocytic leukemia, five (31 percent) had a major hematological response and three (19 percent) had a major cytogenetic response.

- Of nine CML patients in accelerated or blast phase or with

Ph+ALL who also carried the T315I mutation, three (33 percent) had major hematologic response and two (22 percent) had major cytogenetic response.

Researchers also noted responses in patients with heavily resistant disease with no mutations and among patients with other mutations resistant to existing drugs.

The most common side effects were low platelet counts (24 percent of patients), headache (14 percent), nausea (14 percent), joint pain (13 percent), fatigue (13 percent), anemia (11 percent), increased lipase (11 percent), muscle spasms (11 percent), rash (11 percent), muscle pain (10 percent) and pancreatitis (10 percent). All dose-limiting toxicities were reversible.

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