Drug shows promise as new treatment for gut tumor

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A drug that is already an approved therapy for some cancers also might be an effective secondary treatment for a rare tumor of the gastrointestinal tract, according to a team led by researchers from the University of Pittsburgh Cancer Institute (UPCI).

The findings, based on experiments using cell cultures, were published in the Jan. 1 issue of Cancer *Research*.

Bortezomib, or Velcade, is used to treat multiple myeloma and certain lymphomas, said Anette Duensing, M.D., assistant professor of pathology, University of Pittsburgh School of Medicine, an investigator in the Cancer Virology Program, UPCI, and senior author of the study. It works in part by preventing the degradation of certain proteins, which when elevated, induce apoptosis, or programmed cell death, in the cancerous cells.

The researchers suspected that activity could provide an effective way of killing gastrointestinal stromal tumor (GIST) cells. Patients with these tumors are typically treated with imatinib, or Gleevec, and most do very well initially, but complete responses are rare, Dr. Duensing said. There is a need for second- and third-line agents to treat patients whose tumors have become resistant to imatinib. Most GIST patients eventually develop such resistance.

In experiments using a GIST cell line, the researchers found that administration of bortezomib led to cancer cell death through two mechanisms. First, the drug increased the production of a protein called H2AX, which promotes cellular apoptosis. Second, and unexpectedly, the drug also suppressed the cancer cells' production of an enzyme called KIT. Primary mutations in KIT initiate GISTs, and secondary KIT mutations are the driving force behind cancer progression as well as drug resistance in these tumors, Dr. Duensing noted. Importantly, bortezomib also was active against imatinib-resistant GIST cells.

"This is intriguing because resistance to imatinib seems to permit a small pool of quiescent cancer cells to survive," she explained. "But bortezomib eradicates KIT production, so it might be able to rid the body of the remaining tumor cells."

Bortezomib is not presently an appropriate first-line therapy for GIST, she cautioned. But the current findings support moving forward to a clinical trial in appropriate GIST patients to assess its benefits and risks as a secondary treatment.

Provided by University of Pittsburgh