Therapeutic effect of imatinib improved with addition of chloroquine

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The therapeutic effects of the blockbuster leukemia drug imatinib may be enhanced when given along with a drug that inhibits a cell process called autophagy, researchers from the Kimmel Cancer Center at Jefferson reported in the *Journal of Clinical Investigation*.

The cell-death effect of imatinib (Gleevec) was potentiated when chloroquine, an autophagy inhibitor, was given with imatinib for the in vitro treatment of chronic myeloid leukemia (CML) cells including the CML stem cells, according to Bruno Calabretta, M.D., Ph.D., professor of Cancer Biology at Jefferson Medical College of Thomas Jefferson University.

Autophagy is a process that allows cells to adapt to environmental stresses, and enables drug-treated CML cells to escape cell death. Imatinib is a tyrosine kinase inhibitor that suppresses proliferation and induces death of the malignant cells that cause CML. However, additional effects of the drug have not been studied in detail, according to Dr. Calabretta.

In this study, Dr. Calabretta's team, along with Dr. Paolo Salomoni's team from the MRC Toxicology Unit at the University of Leicester in the United Kingdom, found that imatinib induces autophagy in CML stem cells that overexpress a protein called p210BCR/ABL. Stem cells that express this protein have been historically resistant to imatinib and also to second-generation tyrosine kinase inhibitors, including dasatinib, nilotinib and bosutinib.

The autophagy process allows stem cells to survive treatment with imatinib, and continue to survive. The researchers used chloroquine to see if it would have an effect on imatinib treatment. The dual treatment with imatinib and chloroquine eliminated most CML stem cells. Also, imatinib-induced cell death was significantly increased in mice inoculated with p210BCR/ABL-expressing cells.

"Imatinib's primary effect is inhibiting the proliferation of CML cells, but the frequency of resistance increases in advanced stages of the disease," Dr. Calabretta said. "There is a need to develop new therapeutic approaches that, in combination with tyrosine kinase inhibitors, eliminate CML stem cells that escape imatinib treatment. We show that imatinib induces autophagy, which enables these cells to survive and eventually resume proliferation. We also show that chloroquine, an autophagy inhibitor, combined with imatinib actually appears to potentiate imatinib-induced cell death."

Source: Thomas Jefferson University (news : web)