

MAY 20, 2003

Drug-Resistant Cancer Outwitted by Chemical Flank Attack

The drug Gleevec, which has been touted in some circles as a miraculous silver bullet against some forms of leukemia, can still fail in patients who develop mutations that cause the drug to lose effectiveness.

Now, Howard Hughes Medical Institute researchers, working with mice that are genetically programmed to develop resistance to Gleevec, have shown that this therapeutic hurdle can be overcome by administering a second drug that foils the cancer in a novel way. The experiments constitute a proof-of-principle that resistance to Gleevec can be defeated by using a second drug to shut down the activity of the drug's main target, the tyrosine kinase enzyme.

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"Patients with a broad range of cancers that can be blocked by these inhibitors might in the future be treated with 'customized cocktails' of drugs tailored to their specific cancers," said the study's senior author, D. Gary Gilliland, a Howard Hughes Medical Institute investigator at Brigham and Women's Hospital and Harvard Medical School.

In an article published in the May 20, 2003, issue of the journal *Cancer Cell*, Gilliland and his colleagues showed that administering the drug PKC412 effectively thwarts a Gleevec-resistant form of leukemia, called hypereosinophilic syndrome (HES).

Gilliland's collaborators included researchers from the Center for Human Genetics and Flanders Interuniversity Institute for Biotechnology in Belgium, Stanford University School of Medicine, Brown University School of Medicine, Emory University, Dana-Farber Cancer Institute and Novartis Pharma. Lead authors on the paper are Jan Cools, a postdoctoral fellow, Elizabeth Stover, a Harvard Medical School M.D., Ph.D. student, and

Christina Boulton, a student at Harvard Medical School and an HHMI predoctoral fellow, in Gilliland's laboratory.

Gleevec works by inhibiting enzymes called tyrosine kinases. When the activity of tyrosine kinases is unregulated—which can occur when chromosomes improperly exchange chunks of genetic material, creating chromosomal rearrangements—cancer may develop.

Gleevec has proven highly effective in treating chronic myeloid leukemia (CML). And in a recent research article, Gilliland and his colleagues showed that the drug was also effective against HES. Those studied also demonstrated that HES is a form of leukemia.

The current study with PKC412 was prompted when Gilliland and his colleagues identified a patient in their HES study who acquired resistance to Gleevec.

“While this patient did respond to Gleevec,” said Gilliland, “after about three months on the drug, his leukemia began to recur. We were concerned that he had developed a resistance mutation to Gleevec because resistance had been reported in CML patients who had been treated with the drug.”

Gilliland and his colleagues confirmed their suspicions when tests showed that the patient had acquired a mutation in the activated kinase PDGFR-alpha that causes HES. That mutation, they found, was analogous to a mutation that causes Gleevec resistance in CML patients.

“We had preliminary data that PKC412, an alternative tyrosine kinase inhibitor that also inhibits PDGFR-alpha, might overcome resistance to Gleevec,” said Gilliland. He and his colleagues tested their hypothesis both in cell culture and mouse models of leukemia, and showed that the leukemia that was resistant to Gleevec could be cured with PKC412.

“So we infer from these findings that we can either treat Gleevec-resistant patients with PKC412 to treat the resistance mutation; or we could combine the two drugs up front—if they don't have overlapping toxicities—and preclude the development of the resistance mutations,” said Gilliland. Overlapping toxicities might occur if the drugs also inhibited other kinases that when blocked in combination might damage or kill cells. However, initial indications are that toxicity from the combination of two drugs with minimal side effects would probably be modest in comparison to conventional chemotherapy, said Gilliland.

Over the long term, the latest findings that Gleevec and PKC412 show complementary action against kinases bode well for the future development of kinase inhibitors as drugs. “It's a very important point that these two drugs block tyrosine kinase action in different ways,” he said. Furthermore, studies by other researchers have found different resistance mutations in the kinase that causes CML, suggesting that there are many other targets of opportunity for kinase inhibiting drugs.

“It is wonderful that we have a spectrum of inhibitors with different chemical structures - it should be possible to design a custom cocktail of inhibitors to attack tumors caused by any particular tyrosine kinase,” said Gilliland.

Beyond CML, HES and a third major blood disease, acute myelogenous leukemia, other similar malignancies are proving treatable by Gleevec and/or PKC412—including gastrointestinal stromal cell tumors, which are solid tumors, said Gilliland.

“We're very excited about that finding,” said Gilliland. “Our experience in studying hematologic malignancies indicates that the heart of the beast is the proliferative signal, and that not only leukemias but all cancers require such proliferative and survival signals to thrive as tumors. And, if you can target that one genetic lesion, you have a very good chance of having an impact on that tumor.”

Gilliland and his colleagues are conducting genetic screening of the cancers they study to discover activating mutations in kinases. HHMI investigators Bert Vogelstein at The Johns Hopkins School of Medicine and Sanford Markowitz at Case Western Reserve University recently undertook a similar approach and identified new kinase mutations involved in colon cancers.