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Five-Year Study Shows Gleevec's Potency Against Chronic Myeloid Leukemia

In a study of patients with chronic myeloid leukemia, some 95 percent have survived the cancer after five years due to treatment with Gleevec, according to results published this week in the *New England Journal of Medicine*.

Howard Hughes Medical Institute investigator Brian Druker, who led the five-year study, said the findings demonstrate Gleevec's effectiveness against the formerly fatal disease. He noted that the study's results emphasize the value of the new approach to developing cancer drugs that target the specific genetic malfunctions that drive cancer.

Druker, who is at the Oregon Health & Science University Cancer Institute, led an international group of 31 co-authors who published their findings in the December 7, 2006, *New England Journal of Medicine*.

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- **Brian J. Druker**

Druker also led the original clinical development of Gleevec, which inhibits a biological switch called a tyrosine kinase that is abnormally activated in CML. This activation, triggered by an abnormal breakage and rearrangement of a chromosome, drives uncontrolled proliferation of white blood cells. CML is a relatively rare disorder that affects about 5,000 people a year in the United States. Gleevec, marketed by Novartis, is the trade name under which the drug imatinib is sold.

The five-year study followed 553 patients, all of whom were receiving Gleevec as their primary therapy. The study had begun as a comparative study of patients given Gleevec or the previous standard treatment, interferon alfa plus cytarabine. However, the superiority of Gleevec led the researchers to change the study into a long-term assessment of Gleevec's efficacy. The major finding of the study was that only five percent of the patients died from CML during the five-year period, with 11 percent dying from all causes.

The report shows that the drug produced few significant side effects. "The issue of side effects is an important one, because patients with CML need to remain on Gleevec long-term," said Druker. "We found that the incidence of side effects was quite low, and most of the serious side effects occurred in the first year or two of starting therapy." One particular worry, he said, was whether the drug would damage the heart. "We found, however, that only one patient developed heart failure that was thought to be related to the drug, so the risk is incredibly low."

The researchers also found that patients did respond less to Gleevec therapy if they were in a high-risk category due to such factors as an enlarged spleen or a high percentage of immature white cells in their blood. "Even high-risk patients have close to a 70 percent chance of getting to what we call a complete cytogenetic response, which is an optimal response to the drug," said Druker. "That is still six or seven times better than they ever could have hoped for with the previous standard therapy. So, even for high-risk patients, the likelihood of responding is quite high." A cytogenetic response is the measure of the reversion of white blood cells to normal function.

"And more importantly, we found that if a patient achieves a complete cytogenetic response, the risk of relapse is the same whether the patient was at low, medium, or high risk when diagnosed," said Druker. "This finding that Gleevec response trumps the patient's features at diagnosis is critically important, because with the previous standard treatment such a response was not protective from relapse. So, the Gleevec response is, indeed, protective," he said.

Druker said that Gleevec's long-term efficacy also offers a benchmark for comparative testing of two other similar kinase inhibitors, dasatinib and nilotinib, now underway. "If dasatinib or nilotinib can beat Gleevec in the response they elicit, they will offer patients even greater protection from relapse and possibly even better survival," he said.

Druker emphasized, however, that Gleevec and the other kinase inhibitors do not cure CML, they only control it. The researchers' findings showed that there remains a reservoir of aberrant cells that cause the disease to reappear if therapy is stopped. Thus, he said, he and his colleagues are working to understand those cells and how to eradicate them to ultimately cure the disease.

The outcome of the five-year study also offers lessons for physicians who are using Gleevec to treat other cancers, such as gastrointestinal stromal tumor, said Druker. "These findings tell us that we need to treat patients early in the course of the disease," he said. "In CML, there is the advantage that most patients get diagnosed at an early, chronic stage; whereas gastrointestinal stromal tumors are often diagnosed at a more advanced stage. Our results demonstrating Gleevec's high efficacy in CML tell us that in applying the drug to other cancers, we need to diagnose and treat patients earlier in the disease course.

"The lesson from Gleevec for cancer treatment is simple: if you understand what's driving the growth of the cancer and develop a specific drug to target that cause, you can obtain remarkable results," said Druker. "So, these findings should further encourage work toward greater understanding of all the molecular abnormalities in cancer and development of drugs that target those abnormalities."