HUTCH NEWS

# Promising pair

## Drug STI-571 gets two multi-site trials in Clinical Research, PHS as treatment for CML, gastrointestinal-tract tumors

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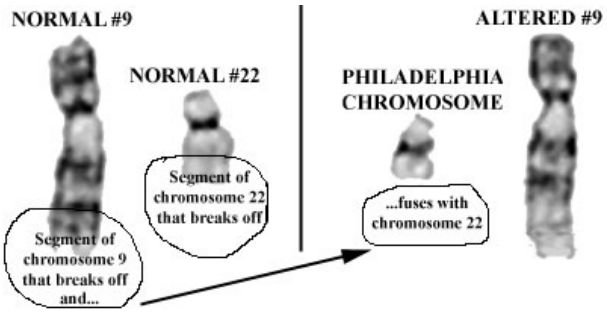


The drug Gleevec - whose effectiveness will be tested by two new Hutch trials - is thought to fight cancer by inhibiting a protein produced by the errant Philadelphia chromosome. A hallmark of CML patients, the Philadelphia chromosome is formed when a segment of normal chromosome 9 fuses to a broken chromosome 22, as shown above. The Philadelphia chromosome has a novel fusion gene, BCR-ABL, which is formed where the breakpoints of the two chromosomes have joined. Drs. Steve Collins and Mark Groudine demonstrated 17 years ago that bcr-abl is expressed at high levels in cells that contain a Philadelphia chromosome.

Hutchinson Center scientists will take part in a pair of multi-site clinical trials to evaluate the safety and efficacy of STI-571 (also known as Gleevec), a drug - taken as a pill - that has shown promise for treating chronic myelogenous leukemia with minimal side effects.

The two studies on this drug involves two Center scientific divisions:

- With a Seattle component led by Dr. Derek Stirewalt of the Clinical Research Division, an international study will compare the effectiveness of Gleevec with standard, non-transplant treatment for CML.
- The Hutch's Southwest Oncology Group, led by Dr. John Crowley of the Public Health Sciences Division, will coordinate a separate trial to evaluate Gleevec as a treatment for soft-tissue tumors of the gastrointestinal tract.

**1,050 patients**

The international study will enroll 1,050 patients in the chronic phase of CML who have been diagnosed within the past six months. It will compare the effectiveness of Gleevec with AraC and interferon, the standard treatment for CML patients who don't receive bone marrow transplants, Stirewalt said.

The project will involve physicians at the Hutch and the University of Washington.

Stirewalt said the phase III trial - a study that evaluates safety and efficacy of a treatment on a large population and compares it to other treatments - will be a crossover study, meaning that patients who don't respond to one treatment will be switched to the comparison therapy.

The five-year trial is funded by Novartis, the drug company that owns Gleevec, and will enroll patients from North America and Australia.

The National Cancer Institute also is helping to develop the drug through a cooperative research and development agreement, a program that fosters collaboration among industry, government and academia to assist in the transfer of federal technologies to the marketplace.

**Only Seattle location**

The Hutch/UW site is the only Seattle-area location offering the trial.

Although Gleevec received widespread attention in the media as a CML therapy, the drug has also shown initial promise as a treatment for cancers that affect the soft tissue, or stroma, of the gastrointestinal tract, Crowley said.

In a second phase III trial, coordinated by SWOG, the Hutch and other cancer centers, including Oregon Health Sciences University, Fox Chase Cancer Center and the Dana Farber Cancer Institute, will test the safety and efficacy of Gleevec on gastrointestinal stromal tumors.

Crowley said that the study will evaluate two doses of the drug in a trial that will involve 600 participants in North America.

Dr. Mike LeBlanc and Diana Lowry, both of SWOG, will serve as the project statistician and data coordinator, respectively.

**Anti-cancer therapy**

Gleevec, initially evaluated by Dr. Brian Druker at Oregon Health Sciences University, acts as an anti-cancer therapy by inhibiting a class of cell-growth proteins called tyrosine kinases.

Tyrosine kinases were discovered initially in their unregulated, or mutant, form as proteins that caused unrestrained cell division, said Dr. Jon Cooper, whose Basic Sciences lab studies the roles of these proteins in normal mammalian cells.

The first oncogene, a cancer-promoting gene, ultimately was determined to be a tyrosine kinase.

"Tyrosine kinases initiate various biological changes in cells when they respond to signals from the outside," Cooper said.

"In the absence of an external signal, these proteins are relatively inhibited in the cell, but it's clear that when they are de-regulated, they can be oncogenic."

Gleevec was identified as a compound that inhibits the bcr-abl protein, a tyrosine kinase produced by white blood cells in CML patients.

Synthesis of bcr-abl is the result of a genetic rearrangement known as the Philadelphia chromosome. In this rearrangement, parts of chromosomes 9 and 22 break off and a portion of chromosome 9fuses to chromosome 22, forming a novel gene. This rearrangement has long been a hallmark of CML.

A different tyrosine kinase, called c-Kit, is produced in abnormal levels in stromal tumors and may be a target for inhibition by Gleevec.

**Useful to basic research**

Cooper said that in addition to their benefit in a clinical setting, drugs like Gleevec that inhibit specific kinases may prove useful for basic scientists who study how kinase signalling pathways are regulated.

Despite the promise of the treatment, Stirewalt cautions against labeling Gleevec a cure for CML.

"Although greater than 90 percent of patients treated with the drug have blood counts that return to normal levels, only 30 or 40 percent of patients have a major cytogenetic response," said Stirewalt, referring to the fact that most patients still retain cells exhibiting the Philadelphia chromosome rearrangement.

Even a few remaining Philadelphia chromosome-positive cells pose a risk for future cancer recurrence, leading some researchers to speculate that Gleevec may need to be administered for prolonged periods, perhaps throughout a patient's life.

**Microarrays**

Stirewalt said future studies by his group will employ microarrays, so-called DNA chips that analyze the regulation of many genes simultaneously, to learn more about Gleevec's mode of action.

"Using microarrays, we plan to examine gene expression patterns from patients before and during treatment with Gleevec to see which genes are affected by the drug," he said.

Such studies may help determine of the optimal time for initiating drug treatment as well as duration of treatment, and may also identify patients most likely to be the best candidates for the therapy