

September 24, 2010 — Treatment with imatinib (*Gleevec*) should not be stopped in patients with advanced gastrointestinal stromal tumors (GIST), because interruption of therapy places them at a high risk for rapid progression of the disease.

This conclusion, published online September 22 in the *Lancet Oncology*, echoes previous findings from studies of chronic myeloid leukemia (CML). In both diseases, all patients benefited from the reintroduction of imatinib, note the researchers, headed by Axel Le Cesne, MD, from the Institut Gustave Roussy in Villejuif, France.

Taken together, these findings support the need for continuous treatment with imatinib and other tyrosine kinase inhibitors — such as nilotinib (*Tasigna*) and dasatinib (*Sprycel*) — in GIST and CML and, by extension, other cancers that are responsive to such drugs, writes Michael Heinrich, MD, from the Portland VA Medical Center and Oregon Health & Science University Knight Cancer Institute, in an accompanying editorial.

"Interruption of treatment is associated with a fairly rapid repopulation of differential cancer cells from an underlying intact population of stem and progenitor cells," Dr. Heinrich explains.

Imatinib is considered to have revolutionized the treatment of both CML and GIST, but the current approach — treatment with tyrosine kinase inhibitors, even the more potent ones — will "not be sufficient to achieve a cure." To achieve that elusive cure, drugs that can eradicate the initiating stem cells will be needed, he notes.

Life-Long Therapy Needed

Elaborating in comments to *Medscape Medical News*, Dr. Heinrich said that for both GIST and CML, it appears that continuous treatment with imatinib or other tyrosine kinase inhibitors is necessary to control the disease.

This means treatment for the remainder of the patient's life. There is currently no alternative — if patients stop taking these drugs, they will die of the disease, he explained.

The average age at diagnosis for both CML and GIST is around 60 years. Before imatinib, the median survival for CML was about 4 years, but this has increased dramatically. "In the imatinib era, it is difficult to estimate the median survival, but it certainly appears to be more than 10 years and perhaps as long as 20 years," Dr. Heinrich said.

"Because these drugs are usually associated with fairly manageable toxicity, it is possible for people to have a very good quality of life, including working full time and being extremely active," he added.

Lead researcher of the study, Dr. Le Cesne, offered similar opinions. It looks as if treatment with tyrosine kinase inhibitors for advanced disease should be continuous. If the patient tolerates the drug well, there are no reasons to interrupt the treatment until progression, he told *Medscape Medical News*. These drugs are usually well tolerated; the patient can often live a normal life and can continue to work, he added.

Dr. Le Cesne and Dr. Heinrich agree that all of these factors should mean that health authorities cover the cost of these "life-long" treatments. But this should not be the case for other anticancer drugs, such as chemotherapies and antiangiogenic drugs in advanced disease, where a normal life is often impossible, Dr. Le Cesne added.

Medical therapy can control disease symptoms and extend life but is not curative.

Tyrosine kinase inhibitors are expensive (costing \$30,000 to \$70,000 per year), but they provide "extremely good results, especially compared with more toxic and less effective therapies," Dr. Heinrich explained.

"The first step in caring for cancer is to convert it to a chronic disease," Dr. Heinrich said. "CML and GIST are among the first cases of cancer for which continuous treatment is necessary. . . . The situation with these diseases is no different from the situation with diabetes or chronic heart disease. In these latter cases, medical therapy can control disease symptoms and extend life but is not curative."

Rapid Progression When Therapy is Stopped

The latest results for imatinib in GIST come from the BRF14 trial conducted by the French Sarcoma Group. This trial originally enrolled 434 patients.

For the current analysis, Dr. Le Cesne and colleagues identified 50 patients with nonprogressive GIST who had been taking imatinib 400 mg/day for 3 years, and randomized them to either continue or stop taking the drug.

After a median follow-up of 35 months, patients who had stopped therapy had a significantly higher risk for rapid progression than those who continued taking the drug. The 2-year progression-free survival was 80% in those who continued taking imatinib, compared with 16% in those who stopped ($P < .0001$).

"Our results show that treatment interruption after 3 years results in tumor progression in most patients," Dr. Le Cesne and conclude.

All but 3 patients in the discontinuation group relapsed, and most of the relapses (17 of 25 patients; 68%) occurred within a year of stopping therapy. Of the 3 patients who did not relapse, 1 had refused to stop imatinib and the other 2 had their tumors resected.

The same group of researchers conducted several other analyses from the BFR14 trial. — they also investigated stopping imatinib after 1 year and after 5 years of therapy. In both cases, stopping treatment led to rapid progression of disease, similar to the findings after 3 years.

"Treatment with imatinib was not sufficient to eliminate the remaining dormant GIST cells and to cure patients with metastatic GIST," they conclude.

Even patients who show a complete response to imatinib (36% of patients before randomization) still have residual disseminated active disease after imatinib treatment, they note. This study shows that it is not safe to interrupt therapy even in these patients, they add.

The reintroduction of imatinib has led to tumor control in all patients that have been assessed so far, the researchers note.

"Very prolonged treatment with adjuvant imatinib may be needed," they conclude, "possibly including life-long treatment."

"Health authorities must consider this new issue," they note, and argue that the "cost of such prolonged treatments can easily be offset by the quality of life of patients with dormant residual tumors."

Dr. Le Cesne reports receiving honoraria from PharmaMar, Pfizer, and Novartis. Several of his coauthors report relevant financial relationships with a number of pharmaceutical companies, as listed in the paper. Dr. Heinrich reports receiving research funding from Novartis and is a consultant to and has equity interest in MolecularMD.

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