Clinical Trial Supports Uninterrupted Use of Gleevec for Gastointestinal Stromal Tumors

People taking Gleevec (imatinib) to treat certain gastrointestinal stromal tumors (GISTs) should continue until the disease gets worse.

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By Edward Winstead

People receiving imatinib (Gleevec) as a treatment for some advanced gastrointestinal stromal tumors (GISTs) should continue the therapy without interruption until the disease gets worse, according to new results from a clinical trial.

The trial, conducted in France, included people with advanced GIST who were treated for 1, 3, or 5 years with imatinib. Participants whose tumors had stopped growing, had shrunk, or had gone away at the end of the treatment period were randomly assigned to continue or stop imatinib until the disease progressed (that is, began to grow or got worse) and were followed for up to 20 years.

The participants who stopped imatinib at the end of all treatment periods experienced a more rapid worsening of the disease, a shorter time until imatinib stopped working (resistance), and did not live as long as participants who continued the therapy, researchers reported in Lancet Oncology on August 7.

These findings affirm expert recommendations that most people with advanced GIST should remain on imatinib therapy without interruption, noted the trial's lead investigator, Jean-Yves Blay, M.D., of Centre Léon Bérard in Lyon, France.

"The discontinuation of imatinib therapy should be discouraged unless there are very good medical reasons to do so," Dr. Blay said.

The authors of an accompanying editorial agreed. If imatinib is working for people with advanced GIST, "don't stop a good thing," wrote Ryan Denu, MD, PhD, and Neeta Somaiah, MD, of the University of Texas MD Anderson Cancer Center.

Conversations about a treatment holiday

Imatinib, a type of treatment known as a tyrosine kinase inhibitor, has long been the standard initial treatment for people with advanced GIST. Although imatinib can shrink tumors, the cancer eventually becomes resistant to the drug and starts growing again.

Other factors that limit how long patients receive imatinib include the cost of the drug and side effects, such as nausea and vomiting, that can affect a person's quality of life, according to the researchers.

Given these issues, "it's natural for patients to have questions about getting a treatment break," said Andrew Blakely, MD, of NCI's Center for Cancer Research, who is a GIST specialist but was not involved in the study.

U.S. and European guidelines generally recommend that patients with advanced GIST continue imatinib indefinitely as long as they can tolerate the side effects of therapy and the disease remains stable. The new findings support this approach while adding additional insights.

The study highlighted the fact "that patients who reach 3 years without disease progression on imatinib have a higher likelihood of better outcomes on long-term imatinib," the editorialists wrote.

"We did not expect the interruption of imatinib to have a detrimental effect on the risk of drug resistance and survival," Dr. Blay said.

All trial results favored uninterrupted treatment

In the clinical trial, called BFR14, the researchers enrolled people with advanced GIST that could not be treated surgically or had spread. All participants began treatment with imatinib and, as long as their cancers didn't start to get worse, stayed on it for at least 1 year. The researchers then randomly assigned patients to continue or discontinue treatment.

They repeated this random assignment for patients who continued to have stable disease after 3 and 5 years of treatment. In all cases, those assigned to stop treatment could resume it if their cancer started to grow again.

The results favored uninterrupted treatment at all time points.

For instance, among the 25 participants who continued imatinib after 3 years of taking it, the median length of time from the date of their random assignment to death from any cause was 11.2 years (134 months), compared with 8.6 years (104 months) in the 25 participants who stopped treatment.

People who took imatinib without stopping lived longer without their cancer getting worse, known

as progression-free survival, than those who stopped treatment. For example, for those who continued imatinib after 1 year of treatment, the median progression-free survival was 27.8 months, compared with 6.1 months among participants who were assigned to stop treatment at that point.

The groups that stopped treatment at each time point developed resistance to imatinib faster than those that continued treatment. For example, for the group that discontinued imatinib after 1 year, the median time to resistance was almost 2.5 years (28.7 months), versus 7.5 years (90.6 months) for the continued treatment group.

More research is needed to understand why resistance develops more quickly in patients who discontinue imatinib, Drs. Denu and Somaiah wrote.

These findings, Dr. Blakely said, can help frame conversations about imatinib therapy between patients and doctors.

“Oncologists could use the new results to explain in detail why extended treatment breaks or stopping the therapy after an arbitrary time point is not usually recommended,” he said.

New insights from long-term follow up of cancer trials

Earlier results from the BFR14 trial had suggested that taking a break from imatinib after 1 year of treatment might be safe for some people with non-progressing, advanced GIST.

“These updated results show the important information that can be learned from following trial participants for long periods,” Dr. Blay said.

A limitation of the trial, the researchers noted, was the small proportion of participants who had their tumors molecularly characterized at the time of randomization and at disease progression. This information could yield clues about the biology of GIST and its treatment.

For patients who are no longer able to receive imatinib, newer tyrosine kinase inhibitors, such as sunitinib (Sutent) or nilotinib (Tasigna), are available. Doctors may select from these next-generation treatments based on the biology of a patient’s tumor.

“We are refining the approach to GIST treatment by taking the specific genetic changes [in a person’s tumor] into account when selecting the next line of therapy,” Dr. Blakely said.

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