

NEWS

New Guidelines Allow Some Patients With Chronic Myeloid Leukemia To Go Off Treatment

By Charlie Schmidt

Most patients with chronic myeloid leukemia (CML) can live out their normal lives by taking tyrosine kinase inhibitors (TKIs). But mounting evidence also shows that roughly a third of those patients can eventually go off treatment altogether without their disease resurging.

Stopping treatment generally hasn't been advised outside clinical trials. But in January, the National Comprehensive Cancer Network, an alliance of 27 U.S. cancer centers, endorsed the practice for selected patients in community settings. European expert groups are moving in the same direction.

TKI cessation could allow patients to save on treatment costs, which in the U.S. often exceed \$100,000 per person. Although eligible patients who discontinue the drugs must be monitored for potential relapses, ending treatment also would allow patients to avoid side effects and costs of therapies they no longer need.

CML occurs when ABL, a gene normally found on chromosome 9, fuses with another gene called BCR on chromosome 22. The aberrant BCR-ABL fusion, also called the Philadelphia chromosome, codes for a protein that causes cells to grow uncontrollably in the blood and bone marrow. By inactivating that protein, TKIs kill mature CML cells and prevent younger stem cells containing the fusion from developing further.

The U.S. Food and Drug Administration approved the first TKI, imatinib, in 2001—transforming CML from a fatal to a manageable condition.

Four more-potent TKIs—dasatinib, nilotinib, bosutinib, and ponatinib—have since become available to treat CML.

Doctors assess how patients respond to the drugs by measuring amounts of BCR-ABL protein remaining in patients' bodies after treatment. The therapeutic goal is a deep molecular response, as defined in an international grading scheme that measures how far levels of BCR-ABL protein fall below pretreatment baselines. A 1,000-fold drop in BCR-ABL protein, for instance, is referred to as molecular response 3.0, or MR3.0 (because 1,000 can be expressed mathematically as 10^3). A 10,000-fold reduction is thus MR4.0.

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Studies of treatment cessation typically restrict enrollment to patients with a sustained MR4.0 or better. At the 2016 annual meeting of the American Society of Hematology in San Diego, researchers presented interim data from the largest cessation clinical trial yet. Called the European Stop Tyrosine Kinase Inhibitor



Michael Mauro, M.D.
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Study, it enrolled 821 patients treated for at least 3 years with imatinib, nilotinib, or dasatinib and had a sustained MR4.0 or better during the final year. Three years after stopping treatment, 38% of the patients

hadn't relapsed. Among the other patients, relapses generally occurred within the first 6 months, underscoring the importance of monthly monitoring during the first drug-free year.

Other studies have generated similar results. In the most recent data from the French Stopping Imatinib Study, for instance, 44 of 100 enrolled patients still hadn't relapsed 77 months after stopping treatment (*J. Clin. Oncol.* 2017;35:298–305; doi:10.1200/JCO.2016.68.2914). “We might ask if these patients haven't been cured of their disease,” said Francois Xavier Mahon, M.D., Ph.D., professor of hematology at the University of Bordeaux in France and a principal investigator on both studies. About a quarter of the patients who discontinue treatment experience a withdrawal syndrome characterized by bone pain and other symptoms that generally resolve within 3 months.

Citing accumulated evidence from more than a dozen cessation trials,

Mahon said success hinges primarily on treatment duration and the length and depth of the molecular response. The new National Comprehensive Cancer Network guidelines call for at least 3 years of TKI therapy and an MR4.0 or better during the 2 years before a patient discontinues the drugs. The guidelines also advise against stopping treatment in patients with any history of accelerated, or blast-phase, CML. Those more advanced stages of the disease are characterized by a higher percentage of the abnormal blood cells also found in the harder-to-treat acute myeloid leukemia.

Cessation also isn't advised for patients who ever developed resistance to imatinib, "no matter how well they did on a different TKI," said Richard Clark, M.D., professor of hematology at Royal Liverpool University Hospital in the UK. The TKIs that became available after imatinib can produce faster, deeper molecular responses, but often with worse side effects. Dasatinib, for instance, can induce

pulmonary hypertension, whereas nilotinib has cardiovascular risks.

Interest in TKI cessation has grown especially among patients who don't easily tolerate the drugs and in women who want to get pregnant. "But some patients are also leery of going off treatment," said Michael Mauro, M.D., clinical director of the Leukemia Service at Memorial Sloan Kettering Cancer Center in New York. "Even patients with undetectable BCR-ABL have 50:50 odds of success, so it's still quite a gamble," he said. According to new data from the DESTINY study in the United Kingdom, halving the TKI dose for a year before cessation "is an option that some patients might be more comfortable with," Clark said. The DESTINY trial enrolled 125 patients with MR3.0 or better and cut their TKI doses in half for a year before stopping treatment. From preliminary results reported at the American Society of Hematology's annual meeting last year, the relapse rate during the reduced-dose phase was only 6.9%.

Nearly all patients who relapse will respond to renewed treatment as they had before cessation. Still, Mauro said, he is worried that in the United States, with its fragmented health care system, patients could be undermonitored. "And they should really be followed for several years," he said.

Researchers are investigating why some patients can go off TKIs successfully, whereas others can't. Evidence suggests that in some patients, going off TKIs after years of treatment induces an immune response that keeps CML stem cells in check. "Even after 5–10 years in the best of cases, we still detect a BCR-ABL fingerprint, but it appears to be under the immune system's control," Mauro said. "We just have to treat patients long enough to get rid of any elements that could cause a relapse. And we need better ways to distinguish who needs continued treatment from who doesn't."

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