Options increase for CML patients failed by existing drugs

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The U.S. Food and Drug Administration (FDA) this month expanded the options for patients with chronic myeloid leukemia and one form of acute lymphoblastic leukemia that carries the Philadelphia chromosome (Ph+ALL). It approved the drug ponatinib (Iclusig), which is effective in a significant number of patients with either disease.

Patients with both leukemias have enjoyed strong responses to imatinib (Gleevec) and second-generation drugs nilotinib (Tasigna) and dasatinib (Sprycel). All work by inhibiting proteins called tyrosine kinases on leukemia cells, in particular the aberrant BCR-ABL protein that causes these diseases.

However, 30-40 percent of CML patients resist imatinib. Nilotinib and dasatinib work for about 40-50 percent of those patients.

"Ponatinib's availability will drastically improve the outcome of most patients with CML and PH+ALL who are resistant or intolerant to prior tyrosine kinase inhibitor therapy," said Jorge Cortes, M.D., professor and deputy chair, in The University of Texas MD Anderson Cancer Center Department of Leukemia.

"Clinical responses to Iclusig have been observed in patients regardless of their mutation status or disease stage. It's a valuable new treatment option for leukemia patients," Cortes said.

New drugs fill gaps in treatment

Ponatinib is the third drug approved by the FDA for CML and Ph+ALL during the past four months, providing oncologists with a wealth of options. Cortes led all of the clinical trials for the three drugs. The other two are bosutinib (Bosulif) and omacetaxine (Synribo). Cortes and other Leukemia Department faculty also led many of the clinical trials for the three previously approved CML therapies.

"It's important to have as many therapies against cancer as we can, because rarely does one drug or combination succeed for all patients," Cortes said. "These new drugs cover different gaps in treatment, so they can serve our patients in different ways," Cortes said. "We hope to have effective treatment options for all of them."

Ponatinib (Iclusig)

Ponatinib, developed by ARIAD Pharmaceuticals, was designed to thwart treatment-resistant mutations. The most prominent is T315I, present in up to 20 percent of patients, which blocks the docking station where other tyrosine kinase inhibitors normally connect to the mutant protein.

In a pivotal phase II clinical trial, which Cortes presented in early December at the 54th American Society of Hematology Annual Meeting and Exposition in Atlanta, ponatinib showed responses against CML at early stage (chronic phase) CML, accelerated phase and blast phase, the most heavily mutated and hard to treat late stage of the disease.

At 15 months of median follow up for patients in the chronic phase of CML, 149 of 267 (56 percent) had a major cytogenetic response (reduction of the cells that carry the Philadelphia-chromosome to 35

percent or less) and 46 percent had a complete cytogenetic response (no cells with the Philadelphia chromosome in the marrow).

Of 64 chronic phase CML patients with the T315I mutation, 45 (70 percent) achieved major cytogenetic response with 66 percent reaching complete cytogenetic response. Patients in the accelerated phase of CML and those in blast phase achieved major hematological responses (major reduction of CML cells in the blood) at rates of 57 percent and 34 percent respectively.

Bosutinib (Bosulif)

Approved by the FDA in September, bosutinib is a second-generation tyrosine kinase inhibitor that works against many BCR-ABL mutations that cause resistance. An important exception is the T315I mutation, which only ponatinib attacks.

"Bosutinib works equally as well as dasatinib and nilotinib," Cortes said. "The significant difference is bosutinib is more specific in its activity, inhibiting BCR-ABL and SRC, but not other tyrosine kinases. This leads to fewer harsh side effects."

There are no issues with cardiotoxicity or pancreatitis, for example, which can arise with other tyrosine kinase inhibitors. "Bosutinib is a good option when we try to choose an appropriate drug for a patient. For those with co-morbidities or other issues, this could be the best fit," Cortes said.

Known commercially as Bosulif, this drug is marketed by Pfizer.

Omacetaxine (Synribo)

Omacetaxine works in a completely different manner from the five tyrosine kinases. It stifles creation of the aberrant BCR-ABL protein, rather than blocking the protein's activity.

"This is an important option for patients who've had several tyrosine kinase inhibitors fail and for those who cannot tolerate those drugs," Cortes said. "A small percentage of patients just need a new approach to get a good response."

Omacetaxine is a synthetic version of a long-time CML drug called homoharringtonine, which is derived from an evergreen tree found in China. While it does not inhibit the activity of the abnormal protein as ponatinib and the other drugs, omacetaxine acts against resistant CML, including T315I mutant, by inhibiting expression of BCR-ABL.

Known commercially as Synribo, this drug is marketed by Teva Pharmaceuticals. Clinical trials combining omacetaxine and tyrosine kinase inhibitors are planned.

Next: Matching drugs to patients, eradicating CML

Before the approval of Gleevec, about half of all CML patients survived to five years. Now 90 percent make it to five years taking the three previously approved drugs. Gleevec and Tasigna are marketed by Novartis, Sprycel by Bristol-Myers Squibb.

Cortes notes important challenges remain. "We need to identify which patients to treat with each drug. Who are the ones I can treat well with imatinib, and who are the patients who need to start with some of the newer drugs?" Cortes said. "Right now, we start everyone with imatinib, dasatinib or nilotinib."

While current drugs reduce CML to extremely low, even undetectable,

levels, most patients must remain on treatment to prevent recurrence. "The idea is to get patients to a certain point where you can stop treatment and know the disease won't come back," Cortes said.

"To achieve this we must develop a tool that reliably tells us that the disease is completely eradicated and treatments effective enough where the majority of patients can be called cured," Cortes said. "There will be a great deal of effort in these two areas now."

Provided by University of Texas M. D. Anderson Cancer Center