

Second-line CML drugs evoke faster, better front-line remissions

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Two drugs approved for treatment of drug-resistant chronic myeloid leukemia provide patients with quicker, better responses as a first therapy than the existing front-line medication, according to two studies published online by the *New England Journal of Medicine*.

Separate international phase III clinical trials compared high-quality remissions after one year of treatment between the standard-of-care drug imatinib, also known as Gleevec®, and the second-line drugs nilotinib (Tasigna®) and dasatinib (Sprycel®). In both trials, previously untreated CML patients who took the newer drugs reached complete cytogenetic response and major molecular response - two important measures of remission -- faster than those taking imatinib. They were also less likely to have their disease progress to advanced stages.

"The second-generation CML drugs are more effective than imatinib and less toxic overall," said Hagop Kantarjian, M.D., professor and chair of The University of Texas MD Anderson Cancer Center's Department of Leukemia. Kantarjian is the corresponding author of the dasatinib study and co-author of the nilotinib study.

Drugs likely to increase survival

"We've learned in [cancer therapy](#) that it's important to use your big guns up front," Kantarjian said. "We know that achieving complete cytogenetic response or major molecular response within a year of

starting treatment is associated with more favorable long-term survival. Using these second-generation drugs first will likely improve outcomes for patients with [chronic myeloid leukemia](#)."

Imatinib, a targeted therapy that blocks the activity of a fusion protein called BCR-ABL that is created by the aberrant Philadelphia chromosome, was a breakthrough drug for CML, nearly doubling the median five-year survival rate for the disease from 50 to 90 percent.

However, 30-40 percent of imatinib patients don't reach a complete cytogenetic or major molecular response, and over time their disease becomes resistant to the drug, Kantarjian said.

(Complete cytogenetic response is the absence of the defective chromosome that causes the disease. Major molecular response is defined as a level of .1 percent or lower of the BCR-ABL oncoprotein as measured by a more sensitive test than traditional cytogenetic analysis.)

Dasatinib vs. Imatinib

In the Dasatinib versus Imatinib Study In Treatment-naïve CML Patients (DASISION) trial, 519 previously untreated CML patients were randomized to either 100 mg of dasatinib once a day or 400 mg of imatinib once a day.

In the dasatinib arm, 77 percent of patients achieved a confirmed complete cytogenetic response (CCyR), 46 percent reached major molecular response (MMR) and 1.9 percent had their CML progress.

Of those receiving imatinib, 66 percent reached complete cytogenetic response, 28 percent major molecular response, and 3.5 percent had their disease progress.

Responses were faster with dasatinib, with 54 percent at CCyR at 3 months and 73 percent at six months compared with 31 percent and 59 percent for imatinib.

Side effects for dasatinib and imatinib were mostly low-grade. Hematologic side effects were slightly more common on dasatinib, while other low-grade side effects such as nausea, vomiting, muscle pain and inflammation were higher on imatinib.

Nilotinib vs. Imatinib

In the Evaluating Nilotinib Efficacy and Safety in Clinical Trials - Newly Diagnosed Patients (ENEST) trial, 836 new CML patients were randomized to either 300 mg or 400 mg of nilotinib twice daily, or to 400 mg of imatinib once a day.

Results in both nilotinib arms of the trial were nearly identical. In the 300 mg twice daily group, 80 percent of patients reached complete cytogenetic response, 44 percent achieved major molecular response and less than 1 percent had disease progression. For the higher dose nilotinib, the numbers were 78 percent, 43 percent and also less than 1 percent.

In the imatinib arm, 65 percent achieved complete cytogenetic response, 22 percent reached major molecular response, and 4 percent had their disease progress.

Patients on nilotinib achieved major molecular response earlier than those on imatinib, with median times to MMR of 5.7 and 5.8 months, compared with 8.3 months for imatinib.

Nilotinib and imatinib had favorable safety profiles, with serious side effects uncommon for either drug. Hematologic side effects - decreased levels of red blood cells, white blood cells or platelets -- were slightly

more common among those on imatinib. Nausea, diarrhea, vomiting, muscle spasms and edema were higher on imatinib, but rash, headache, hair loss and itching were higher on nilotinib.

Novartis, the company that makes imatinib, also developed nilotinib, and Bristol-Myers Squibb developed dasatinib, both of which are more potent inhibitors of the BCR-ABL protein. The two drugs are approved as second-line therapy after imatinib fails or as first therapy for those who cannot take imatinib. Both companies are expected to seek U.S. Food and Drug Administration approval for the two drugs as initial therapy for CML.

"Findings from both of these studies confirm the single-arm trials done at MD Anderson, which had shown superiority of second-generation drugs in a front-line setting," Kantarjian said. The two ongoing single-arm clinical trials, led by Jorge Cortes, M.D., professor in MD Anderson's Department of Leukemia, compare the performance of the drugs in new patients to historical results from earlier trials of imatinib.

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

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