Second-generation CML drugs show promise as frontline therapy

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Two drugs approved as fallback therapy for chronic myelogenous leukemia (CML) appear to outperform historical benchmarks of the frontline medication when used as a first treatment in separate clinical trials, researchers at The University of Texas M. D. Anderson Cancer Center reported at the 50th Annual Meeting of the American Hematological Society.

Frontline therapy for CML remains imatinib, a Novartis drug known as Gleevec® and a major success story in targeted cancer treatment that has increased the five-year survival rate for the disease from 50 percent to 90 percent of patients.

"We are seeing more patients achieve complete cytogenetic responses faster with either drug than we did during clinical trials with imatinib," said Jorge Cortes, M.D., professor in M. D. Anderson's Leukemia Department and leader of both studies. "These are early but encouraging results."

Complete cytogenetic response is the absence of the defective chromosome that causes the disease. Cortes and colleagues compare current clinical trial results to M. D. Anderson's extensive historical results from earlier trials of imatinib.

Researchers are comparing nilotinib, a Novartis drug known as Tasigna®, and dasatinib, a Bristol-Myers Squibb drug known as Sprycel®, to imatinib. Both are approved by the U.S. Food and Drug

Administration for patients who can't tolerate imatinib or whose CML resists the drug.

The nilotinib trial has enrolled 49 patients with previously untreated early stage CML, and some with second stage disease. The 400mg twice daily dose led to complete cytogenetic response in nearly all patients as early as three months into the trial.

Overall, 44 of 46 (96 percent) evaluable patients have achieved a complete cytogenetic response at some point during the trial. At one year, 52 percent achieved a major molecular response, an even more stringent measure of disease remission.

The dasatinib trial has enrolled 50 patients with previously untreated early stage CML taking either 50 mg twice daily or 100 mg once a day. Overall, 44 of 45 patients (98 percent) have achieved complete cytogenetic response at some point during the trial. At one year, 34 percent have achieved major molecular response.

While both dasatinib and nilotinib have so far outperformed a 400mg daily dose of imatinib at all times, longer-term results are converging with those seen with an 800 mg daily dose of imatinib.

Both clinical trials continue to enroll patients. Side effects are being closely monitored and some patients in each trial had their doses reduced or treatment temporarily interrupted to deal with toxicities. "Side effects so far are manageable and comparable to those seen with imatinib," Cortes said.

Imatinib targets the aberrant Bcr-Abl protein, caused by a chromosomal abnormality called the Philadelphia Chromosome, which fuels an overabundance of white blood cells and immature stem cells called blasts that crowd out red blood cells and platelets. Nilotinib and dasatinib

target a greater variety of genetic variations leading to CML and often work after imatinib has failed.

The clinical trials are funded by Novartis and Bristol-Myers Squibb who provide both study medicines for off-label use.

Source: University of Texas M. D. Anderson Cancer Center