Drug Developers Unveil Strategies Aimed at Imatinib-Resistant CML

By Merrill Goozner

With the arrival of imatinib (Gleevec) a decade ago, chronic myelogenous leukemia (CML) turned into a chronic disease. Clinicians hailed its estimated 85% success rate in the rare but deadly cancer as a triumph for the new field of targeted therapeutics. Last year, Brian Druker, M.D., of Oregon Health Sciences University, who persuaded Novartis to pursue development of imatinib and ran its pivotal clinical trials, received the prestigious Lasker-DeBakey Award for Clinical Medical Research for his decades-long quest to come up with a successful drug for the condition.

However, one in seven CML patients did not respond to initial imatinib therapy, and they were soon joined by a small group who developed resistance, estimated at 10%–15% of patients who initially benefited from the drug. Resistance usually developed in the first 5 years of taking the tyrosine kinase inhibitor (TKI). U.S. Food and Drug Administration approval of follow-on TKIs for treating CML—dasatinib (Sprycel) from Bristol-Myers Squibb in 2006 and nilotinib (Tasigna) from Novartis in 2007—offered alternatives for some, but not all, of those patients.

One group that did not respond to any TKIs were patients who had developed the T315→I mutation of the BCR-ABL gene on the abnormal Philadelphia chromosome that causes the disease. An estimated 2%–3% of patients—about 200 people a year in the U.S.—develop the drug-resistant T315→I mutation.

In recent months, drug developers have unveiled several strategies for dealing with the T315→I mutation. One seeks to restrict its emergence by limiting overall resistance. Another would treat it with a new chemotherapy agent. Others are working on new drugs that will target the mutation.
Meanwhile, basic scientists are studying the quiescent bone marrow stem cells that are thought to lead to CML to identify new targets for drugs that could eradicate the disease, because TKIs must be taken for life. “Imatinib doesn’t sufficiently target the CML stem cell,” said Robert Redner, M.D., associate professor of medicine at the University of Pittsburgh, who recently reviewed those potential pathways for The Oncologist.

**Treat Up Front, Limit Resistance**

Novartis is pursuing a “limit resistance” strategy. Later this year, the FDA will consider its application to make nilotinib first-line therapy for CML on the basis of a clinical trial unveiled at last December’s American Society of Hematology meeting in Orlando. Early-stage trials of both nilotinib and dasatinib had indicated that they might be more potent inhibitors than imatinib because they hit more of the estimated 50 known tyrosine kinase mutations that can occur in the BCR-ABL gene.

The recent trial, sponsored by Novartis, directly compared TKI-naïve CML patients treated with nilotinib and imatinib. It confirmed a statistically significantly higher response rate in the nilotinib group.

The 846 patients were randomized to receive either a 300- or a 400-mg dose twice a day of nilotinib or a 400-mg dose once daily of imatinib. After a year, less than 1% of patients in the nilotinib groups had advanced from the chronic phase of the disease to the accelerated or blast phase, either of which signals treatment failure and usually leads to death. Nearly 4% in the imatinib arm advanced.

Moreover, the patients in the nilotinib arms had statistically significantly higher molecular and cytogenetic response rates, which are surrogate markers for risk of disease progression. The markers showed a reduction in cancerous cells to near-undetectable levels in the blood and bone marrow. The cytogenetic response rates at 12 months were 80% (300 mg) and 78% (400 mg) in the nilotinib arms compared to 65% in the imatinib arm, according to the study abstract presented at the Orlando meeting. The study also yielded evidence that patients in the nilotinib arm experienced some reduced side effects associated with TKI therapy. For instance, about 10% suffered neutropenia from the drug, compared with 20% in the imatinib arm.

Though neither drug affected the T315→I mutation, company officials believe that better treatment at the outset of TKI therapy will reduce the number of people who eventually develop untreatable resistance. “Our approach was to come up with a better up-front treatment for those patients who don’t do well in the first few years,” said Laurie Letvak, M.D., vice president of Novartis’ global program for imatinib and nilotinib. “Should we design a drug for a troublesome mutation? That’s a nearly impossible task since there will always be another troublesome mutation.”

FDA approval of nilotinib as first-line therapy, should it occur, will be a financial boon to Novartis. Nilotinib generated nearly $4 billion in sales for Novartis last year compared with just $68 million for imatinib, but the imatinib patent expires in 2015. Nilotinib’s patent doesn’t expire until 2023.

Not everyone agrees that nilotinib represents an important advance over imatinib treatment. Great Britain’s National Institute for Health and Clinical Excellence (NICE) last November rejected paying for nilotinib and dasatinib once patients have had to stop taking imatinib because of either resistance or intolerance of its side effects. In February, NICE’s advisory committee reaffirmed that conclusion for the intolerant group but agreed to reconsider the resistant group in light of more recent evidence.

However, the head reviewer didn’t hold out much hope that the drugs would be approved for sale in the UK when it makes its final decision later this year, largely because the incremental benefit of using a different TKI after resistance emerges was low. “The committee noted that the evidence was very poor—observational studies without simultaneous comparators,” said Peter Littlejohns, MBBS, clinical and public health director for NICE. “The committee did feel there was an added benefit, but the price being set so high, the opportunity costs of spending the money on these patients wouldn’t be a cost-effective use of these funds.”

**Block the T315→I Mutation**

Some drug developers believe that the T315→I mutant may prove difficult to block with any TKI. CytRx, a small Los Angeles–based drug development company, recently reported a phase I clinical trial for a new TKI aimed at imatinib-resistant CML and other cancers. The drug, dubbed INNO-406, inhibits both the ABL and the LYN tyrosine kinases. The positive results encouraged company officials to begin second-phase trials in imatinib-resistant CML patients and in people with chronic lymphocytic leukemia, glioblastoma multiforme, and hormone refractory prostate cancer that has stopped
responding to androgen deprivation therapy.

But according to company officials, the experimental drug did not affect the four of 56 patients in the trial who tested positive for the T315→I mutation. “That was the only mutation that we didn’t show activity against,” said Daniel Levitt, M.D., chief medical officer for CytRx. “We were active against all the other variants. I’m not a molecular biologist, but I think this mutation is really far outside the area that’s basically blocked by these drugs.”

Whereas TKI manufacturers’ strategic approach is to reduce overall resistance, a small Australian company is tackling the T315→I problem head on. ChemGenex in late March sought approval from the FDA and its Oncology Drugs Advisory Committee for the first chemotherapy drug specifically targeted at the mutation. Omacetaxine mepesuccinate (Omapro), a plant-derived drug that originated in the National Cancer Institute, showed some marginal efficacy against the mutation in a 66-person trial.

But the FDA reviewers criticized the company’s application, in part because only 25% of patients (by the company’s calculations) and 15% (by the FDA’s) responded to the highly toxic injectable drug for a mean duration of 7.7 months. The federal agency discounted the efficacy results because the company failed to provide a validated assay for measuring the presence of the T315→I mutation in one-third of the patients included in its trial, casting doubt on nearly half the positive responses. On the bright side, the company’s efforts to reverse the FDA’s decision could be a boon to other companies seeking to develop drugs for resistant strains of CML.

Still, clinicians want something better than a toxic chemotherapy drug for third-line therapy. “It is at best a modest advance, but it does offer patients with T315→I something besides stem cell transplant, as there are currently no other effective therapies,” said Druker in an e-mail. “As soon as oral T315→I inhibitors are available, it will be largely replaced, given the non-specific mechanism of action and side effects.”

But is targeting T315→I the best way to go? Redner’s review of recent developments suggested targeting what he called leukemia-initiating cells in bone marrow as the more promising path for eliminating all variants of CML. “These cancer-initiating cells have been identified as playing a role in many malignancies, including CML,” he wrote. “Cancer stem cells seem to be more resistant to conventional therapy and so are able to survive in small numbers and repopulate the malignancy.”

Still unknown is whether imatinib suppresses CML stem cells below the level of detection, leaving some resistant cells to grow back, or if the drug does not affect the stem cells that lead to CML at all. “Although CML progeny cells may become resistant to imatinib through selection of mutated clones, there is evidence to suggest that not only may [leukemia-initiating cells] be inherently resistant but imatinib itself may [also] induce resistance,” he wrote.

Redner concluded his review with the suggestion that targeting genes that are overexpressed in CML stem cells may be a potential strategy for eradicating the disease. His list of potential targets included the Wnt pathway, which is critical to stem cell growth; the PML tumor suppressor gene; and the NF-κB pathway, which is also important for CML stem cell growth.