With Targeted Drugs, Chronic Myelogenous Leukemia Therapy May Follow HIV’s Model

By Rabiya S. Tuma

The targeted therapy imatinib has been a major success for many patients with chronic myelogenous leukemia (CML). Recently the U.S. Food and Drug Administration (FDA) approved a second targeted agent, dasatinib, for CML patients who don’t respond to imatinib.

That makes CML the first cancer to have two targeted agents that are effective enough to be used alone. And more agents are in the works. With such riches, leukemia specialists are trying to figure out how best to use the agents: alone, in sequence, or together.

As more and better targeted drugs are developed for other cancers, the researchers’ efforts in CML may serve as a model for how to move forward in similar situations in the future. Some experts suggest that the model already exists.

“The reality is that we already have that paradigm with HIV [human immunodeficiency virus], and we are just reinventing it with cancer,” said Brian Druker, M.D., professor at the Oregon Health and Science University in Portland who developed imatinib. “That is good news. If you look at survival rates for HIV, they are pretty remarkable with triple-drug therapy. I don’t see why cancer shouldn’t or couldn’t be the same if you understand the targets and resistance mechanism.”

The key, he said, is to identify the mechanisms of resistance to the first drug and then develop second generation agents that block that resistance. “Then you think about combination and sequential therapy.”

Dasatinib Data

Imatinib’s effectiveness has been shown again recently. Data published late last year in the New England Journal of Medicine show that imatinib remains effective for many CML patients even after 5 years of therapy. Specifically, the researchers found that 89% of 553 CML patients treated with imatinib are still alive after 5 years. The outcome was best for the imatinib patients who achieved a complete cytogenetic response after 12 months, with 97% remaining relapse free at 5 years.

Unfortunately, not all patients respond equally well to imatinib, and some cannot tolerate it from the start. With that in mind, researchers have been working on several second-generation inhibitors, including dasatinib and nilotinib (formerly AMN107), which is in late-stage clinical testing.

Imatinib and the other newer agents designed to treat CML inhibit the activity of the Bcr-Abl fusion gene, which is formed by a chromosomal translocation that results in the Philadelphia chromosome, the hallmark of CML. Each of the agents differs in its molecular structure, how it binds to the Bcr-Abl protein, and what other tyrosine kinase proteins it inhibits. Those differences lead to different patterns of activity and resistance.

Dasatinib gained FDA approval last summer on the basis of five phase II trials that tested the drug in several different stages of CML, as well as in Philadelphia chromosome-positive acute lymphoid leukemia (Ph+ ALL). All the patients in the trials were either intolerant of imatinib or had not responded to it. With dasatinib, 90% of chronic-phase patients achieved a complete hematologic response, and 45% had a major cytogenetic response—less than 35% of the patients’ bone marrow cells carried the abnormal Philadelphia chromosome. In the more advanced-stage CML and in Ph+ ALL, 31%–59% had a major hematologic response, 24%–33% of patients had a complete hematologic response, and 30%–58% had a major cytogenetic response.

In a small randomized phase II trial, patients who had chronic CML that was resistant to the standard dose of imatinib appeared to do better on dasatinib than on high-dose imatinib. Of 22 patients randomly assigned to dasatinib, 95% had a complete hematologic response and 45% had a major cytogenetic response, which is associated with better clinical outcomes. By comparison, 93% of the 11 patients assigned to high-dose imatinib had a complete hematologic response, and 21% had a major cytogenetic response.

These data show that dasatinib, like imatinib, is highly effective as a single agent. Moreover, that dasatinib can induce a complete cytogenetic responses in some patients who have previously progressed on imatinib is remarkable, say some experts, and suggests that the newly approved agent might be superior. However, proving that will be difficult in previously untreated patients because of the long-term efficacy data already available for imatinib.

Which Drug for First-line?

Which drug to use for previously untreated patients, in fact, is the key question facing CML clinical researchers now. Researchers are choosing between two approved agents, both relatively nontoxic. Currently, only imatinib is approved for these patients, but both Druker and Charles Sawyers, M.D., chair of the human oncology and pathogenesis program at Memorial Sloan-Kettering Cancer Center in New York, think there are reasons that dasatinib might be the better agent.

Dasatinib binds the Bcr-Abl protein 300 times more tightly than imatinib, meaning that a lower dose is needed to achieve the same degree of target inhibition. It also binds both the inactive and active forms of the protein, while imatinib binds only to the inactive one. Thus, mutations that affect the active form may lead to imatinib resistance. Also, dasatinib blocks Src kinase activity, which Shaoguang Li, M.D., of the
Jackson Laboratory in Bar Harbor, Maine, recently showed becomes activated by the Bcr-Abl protein and may be important in CML disease progression. Dasatinib appears to induce complete cytological remission in patients more quickly than imatinib, Druker said, which could minimize the growth of drug-resistant clones.

However, the only sure way to find out which drug is better is to do a head-to-head comparison. A small pilot study with 240 patients has been designed by several cooperative trial groups and will start enrolling patients early in 2007. However, it is designed to look only at response rates and tolerability. “It is not powered to look at all at survival,” Druker said, and thus will not provide a definitive answer.

Moreover, a trial comparing the drugs’ success in progression-free or overall survival is unlikely. A trial would have to run at least 5 years because of the low relapse rate on imatinib, and rates on dasatinib are likely to be the same or better, Sawyers said, which means that a trial would be expensive. “It is not justifiable to answer that question, even though it is interesting.”

**Combination Therapy?**

A pressing question is whether sequential therapy is the right approach, or whether the agents would be more effective in combination right from the start. Resolving this question requires looking at the resistance patterns among imatinib and dasatinib patients.

Researchers have identified up to 40 mutations in the Bcr-Abl protein that cause imatinib resistance. All but one—T315I, a threonine-to-isoleucine amino acid substitution at residue 315 in the Bcr-Abl protein—remain sensitive to dasatinib. By contrast, Druker estimated that only five to 10 mutations are responsible for dasatinib resistance, with about half remaining sensitive to imatinib.

In one study, presented at the American Society of Hematology meeting in December by Neil Shah, M.D., of the University of California in San Francisco, three mutations accounted for dasatinib resistance in 15 patients tested. The T315I mutation again proved important, with 11 patients carrying it. Those patients were also imatinib resistant. The problem is that patients, such as those in Shah’s study, first develop mutations that cause imatinib resistance and then gain more mutations that cause dasatinib resistance. These compound mutations leave physicians and patients without good treatment options given existing therapies, and they form the prime argument for starting patients off on a combination of imatinib and dasatinib. With both agents, the likelihood that compound mutations would arise is substantially reduced, at least in theory.

With that in mind, Sawyers, Shah, and others, with support from dasatinib maker Bristol-Myers Squibb, have launched a phase I trial to test the feasibility of the combination. Although no data are available, anecdotal reports from one patient treated off study with the imatinib and dasatinib combination hints that the combination is tolerable despite having many shared targets beyond Bcr-Abl, Sawyers said.

Many patients appear hesitant to enroll in the trial, he said. The target population is patients who have shown a partial response to imatinib but are not doing optimally on it and so are more likely to suffer a relapse, relative to those with a complete cytogenetic remission. Also, last summer’s report of cardiac problems associated with imatinib or dasatinib, published in *Nature Medicine*, seems to have frightened patients, though neither Sawyers nor Druker has seen evidence of problems.

“I can’t precisely blame [the article], but they are all asking, ‘Well, I’m already on one and you want to add another. Will it hurt my heart?’” he said. “There is not a compelling reason for them to participate because they are doing pretty well, just not great. There is no emergency.”

“Their hesitation may prove to be a stumbling block for researchers trying to develop combinations in the era of targeted agents that work as well as monotherapy.”

**The T315I Problem**

There are technical problems as well. Using imatinib and dasatinib in sequence in patients with advanced disease appears to induce development of the T315I mutation, which makes it resistant to both agents. And patients with Philadelphia-positive ALL or advanced-stage CML who have been previously treated with imatinib respond to nilotinib and dasatinib for only a relatively short period. “Both of them appear to exert enormous selection pressure for the T315I phenotype, said Francis Giles, M.D., of the University of Texas M. D. Anderson Cancer Center in Houston.” No combination of imatinib, dasatinib, and nilotinib can block the development of that mutation, so agents that can inhibit it are needed.

One candidate is MK-0457 (formerly VX-680), which is already in phase I trials for patients with blood cancers. The drug was being developed for other uses when Sawyer’s group, then at the University of California in Los Angeles, found that the drug inhibited the T315I mutant Bcr-Abl protein. Forty patients have been treated in the phase I trial, including 15 with accelerated or blast phase CML. All 11 CML patients who carried the T315I mutation showed an objective response to the drug, Giles reported at ASH in December. One patient has had 15 cycles of therapy, over approximately 7.5 months, and continues to respond. (By contrast, in the phase II trials used for dasatinib’s regulatory approval, most patients with blast crisis disease relapsed within 6 months.)

MK-0457 appears to be well tolerated, although it is more like a traditional chemotherapy agent than any of the other anti-Bcr-Abl agents; MK-0457’s toxic effects include nausea, skin rash, and water retention. It is delivered by a 5-day continuous infusion and appears to induce dose-dependent bone marrow suppression, as well as hair loss.

“While it may not be as perfect an idea as imatinib or dasatinib, it certainly makes it clear that compounds that can inhibit T315I are out there,” Sawyers said. “I know of at least 10 in various stages of development.”
Preclinical data for several similar agents were also presented at ASH, though thus far, clinical data appear to be available only for MK-0457.

If MK-0457 or other drugs prove effective against T315I CML clones, then an obvious approach would be to combine them with already approved agents. In fact, Merck plans to launch a phase II trial in January 2007, which Giles referred to as a “pivotal single-agent study,” for patients with T315I or for patients who have failed to respond to dasatinib or nilotinib. Giles also said that plans are in the works to initiate a combination trial with dasatinib and MK-0457 later in 2007 and another with nilotinib as soon as it is approved.

Affordability Question
The biological arguments for using a combination of targeted therapies are strong, but can anyone afford the treatment? Bristol-Myers Squibb, which makes dasatinib, says the wholesale price for the drug is $3,900 per month for a CML patient. Novartis, which makes imatinib, says a standard dose of that drug costs $2,600 per month for CML treatment. Neither Druker nor Sawyers is readily willing to jump on board for a $78,000-per-year therapy for a chronic condition, but neither sees such a high price as the only possible outcome of combination therapy. (Both researchers were involved in clinical trials of these companies’ drugs at their institutions, but neither gets direct compensation.)

“I think you could argue that the risk of relapse justifies the expense of combination therapy,” Sawyers said. “On the other hand, it might be that the combination would induce such a deep remission that you wouldn’t need continuous therapy.” If, for example, some combination of these agents is effective against leukemia stem cells, it might allow a patient to be on therapy for a finite period of time, as opposed to the continuous therapy that is required for imatinib now. “In which case you might save money,” he said.

Druker appears to be relying less on changing biology and more on a changing marketplace to mitigate drug costs. “Novartis and Bristol-Myers are going to start competing. Right now [imatinib and dasatinib] are priced relatively similarly, but if a third one comes into the market then all of these companies are going to look at where is their place and how are consumers, including physicians, going to factor cost into all of this.”

Although this prediction may sound unduly optimistic, he points to other drugs and disease arenas. For statins and nonsteroidal antiinflammatories, “only the new drugs are premium priced, and it is not clear that they are that much better.” Also, as researchers get better at selecting patient populations for targeted agents, clinical trials should be smaller and costs lower. Considering these factors, “I don’t worry so much about drug pricing,” Druker said. “I think right now we are in an era where drug pricing is certainly outlandish, but I view that as a temporary problem.”

That seems to be what has happened with anti-HIV drugs. Prices have declined with the introduction of highly active anti-HIV therapies, a shift from acute to chronic therapy, and more available drugs. They may not be cheap, but society seems to agree that they are affordable.

The issue of cost, however, becomes relevant only if combination therapy proves to be the right way to go, and that is a question that only the upcoming clinical trials can answer.